



# **Tirzepatide for Type 2 Diabetes**

**Final Report**

**February 15, 2022**

**Prepared for**



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## List of Acronyms and Abbreviations Used in this Report

|          |  |
|----------|--|
| AACE     | American Association of Clinical Endocrinologists            |
| ACCORD   | Action to Control Cardiovascular Risk in Diabetes            |
| ACE      | American College of Endocrinology                            |
| ADA      | American Diabetes Association                                |
| AE       | Adverse event  |
| ASCVD    | Atherosclerotic cardiovascular disease                       |
| BL       | Baseline   |
| BMI      | Body Mass Index  |
| bpm      | Beats per minute   |
| BT       | Background therapy   |
| CEPAC    | Comparative Effectiveness Public Advisory Council            |
| CGM      | Continuous glucose monitor                                   |
| CHF      | Congestive heart failure                                     |
| CI       | Confidence interval  |
| cm       | Centimeter   |
| CKD      | Chronic kidney disease                                       |
| CR       | Credible range   |
| CV       | Cardiovascular   |
| CVD      | Cardiovascular disease                                       |
| CVO      | Cardiovascular outcomes                                      |
| CVOT     | Cardiovascular outcomes trial                                |
| DBP      | Diastolic blood pressure                                     |
| D/C      | Discontinuation  |
| dL       | Deciliter  |
| DPP-4    | Dipeptidyl peptidase-4                                       |
| DTSQc    | Diabetes Treatment Satisfaction Questionnaire change version |
| DUA      | Dulaglutide  |
| Dx       | Diagnosis  |
| EASD     | European Association of the Study of Diabetes                |
| eGFR     | Estimated glomerular filtration rate                         |
| ESC      | European Society of Cardiology                               |
| evLY     | Equal value of life years                                    |
| evLYG    | Equal value of life years gained                             |
| EMPA     | Empagliflozin  |
| ER       | Emergency room   |
| ESRD     | End-stage renal disease                                      |
| ETD      | Estimated treatment difference                               |
| FDA      | Food and Drug Administration                                 |
| FPG      | Fasting plasma glucose                                       |
| GIP      | Glucose-dependent insulintropic polypeptide                  |
| GLP-1    | Glucagon-like peptide 1                                      |
| GLP-1 RA | GLP-1 receptor agonist                                       |
| HbA1c    | Hemoglobin A1c/glycosylated hemoglobin                       |
| HDL      | High density lipoprotein cholesterol                         |
| HF       | Heart failure  |
| HFpEF    | Heart failure with preserved ejection fraction               |
| HFREF    | Heart failure with reduced ejection fraction                 |
| HR       | Hazard ratio   |
| HUI-3    | Health Utilities Index Mark 3                                |
| ICER     | Institute for Clinical and Economic Review                   |



|               |  |
|---------------|--|
| IGlar         | Insulin glargine   |
| IWQOL-Lite-CT | Impact of Weight on Quality of Life-Lite Clinical Trials Version   |
| ITT           | Intention to treat   |
| kg            | Kilogram   |
| LDL           | Low density lipoprotein cholesterol                                |
| LOCF          | Last observation carried forward                                   |
| LYG           | Life years gained  |
| m             | Meter  |
| MACE          | Major adverse cardiovascular event                                 |
| MACE-3        | 3-point MACE   |
| MACE-4        | 4-point MACE   |
| MAR           | Missing at random  |
| MET           | Metformin  |
| mg            | Milligram  |
| MI            | Myocardial infarction  |
| mITT          | Modified intent to treat   |
| mL            | Milliliter   |
| MM            | Mixed-effects model  |
| mmol          | Millimole  |
| mmHg          | Millimeter of mercury  |
| MMRM          | Mixed-effects model repeated measures                              |
| mol           | Mole   |
| MTD           | Maximum tolerated dose   |
| n             | Number of subjects with events                                     |
| N             | Number of subjects in full analysis set                            |
| NA            | Not applicable   |
| NHANES        | National Health and Nutrition Examination Survey                   |
| NICE          | National Institute for Health and Care Excellence                  |
| NR            | Not reported   |
| NMA           | Network meta-analysis  |
| NON           | Noninferiority   |
| OM2           | Outcomes Model 2   |
| OR            | Odds ratio   |
| OSEM          | Oral semaglutide   |
| OW            | Once weekly  |
| OWSA          | One-way sensitivity analysis                                       |
| PBO           | Placebo  |
| PICOTS        | Population, Intervention, Comparator, and Study Design             |
| PK            | Pharmacokinetics   |
| PRISMA        | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PRO           | Patient reported outcome   |
| QALY          | Quality-adjusted life year   |
| QW            | Once weekly  |
| RA            | Receptor agonist   |
| RCT           | Randomized controlled trial  |
| REF           | Reference  |
| SBP           | Systolic blood pressure  |
| SD            | Standard deviation   |
| SEM           | Semaglutide (injectable)   |
| SF-36         | Short Form Health Survey   |
| SGLT-2        | Sodium-dependent glucose co-transporter-2                          |
| SITA          | Sitagliptin  |

|        |  |
|--------|--|
| SU     | Sulfonylurea                                 |
| TEAE   | Treatment emergent adverse event             |
| T2DM   | Type 2 diabetes mellitus                     |
| Tx     | Treatment                                    |
| TZD    | Thiazolidinedione                            |
| TZP    | Tirzepatide                                  |
| UKPDS  | United Kingdom Prospective Diabetes Study    |
| US     | United States                                |
| USD    | United States dollar                         |
| USPSTF | United States Preventive Services Task Force |
| VAS    | Visual analogue scale                        |
| WAC    | Wholesale acquisition cost                   |

# Executive Summary

---

Type 2 diabetes mellitus (T2DM) is characterized by the progressive loss of adequate insulin secretion from the pancreas and peripheral insulin resistance. It affects more than 34 million Americans, with minorities bearing a disproportionate burden of disease.<sup>1</sup> Chronic exposure to high blood glucose levels may damage both small (microvascular) and large (macrovascular) blood vessels, and can result in complications such as blindness, chronic kidney disease (CKD), and atherosclerotic cardiovascular disease (ASCVD). Consequently, the annual costs associated with T2DM exceeded \$300 billion in 2017.<sup>2</sup>

Patients with T2DM described the struggle of managing their disease, including struggles with glycemic control, losing weight, managing comorbidities and disease complications, and the expense of medications. Early, comprehensive, culturally tailored education about diabetes self-management, along with access to and affordability of medications, were identified as critical factors in the success of managing T2DM over a patient's lifetime.

A measurable short-run goal of treating T2DM is glycemic control, with a goal glycated hemoglobin (HbA1c) of <7.0% in most patients.<sup>3</sup> Beyond lifestyle modifications, metformin is recommended as first-line therapy in most patients.<sup>4</sup> Additional therapy is indicated if glycemic goals are not met with metformin alone. For patients with or at high risk of ASCVD, heart failure, or CKD, sodium glucagon-like peptide-1 receptor agonists (GLP-1 RA) or glucose transporter-2 (SGLT-2) inhibitors – with or without metformin – are preferred due to favorable cardiovascular and renal outcomes data.<sup>4</sup>

Even with current treatment options, nearly half of T2DM patients may not have adequate levels of glycemic control.<sup>1</sup> Tirzepatide (Eli Lilly), a novel, once-weekly injectable dual glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 RA combination drug, has been developed to treat patients with T2DM. A biologics license application with priority review was submitted to the FDA for T2DM on October 27, 2021, with a decision expected in mid-2022.

We compared the clinical and cost effectiveness of tirzepatide added on to background therapy compared with background therapy alone, or injectable semaglutide (Ozempic®, Novo Nordisk) or empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly) added on to background therapy. Treatment with tirzepatide 15 mg resulted in a statistically significant decrease in HbA1c of 2.5% and in weight of 10.9 kg compared with background therapy.<sup>5</sup> Gastrointestinal symptoms were the most common adverse events; severe hypoglycemia was rare.

Tirzepatide also showed a greater reduction in HbA1c, weight, triglycerides, and blood pressure when compared head-to-head with injectable semaglutide in a Phase 3 randomized controlled

trial.<sup>6</sup> However, the tirzepatide group had a greater incidence of gastrointestinal side effects, severe adverse events, and discontinuation compared with semaglutide.

Due to a lack of head-to-head trials, tirzepatide and empagliflozin were compared through a network meta-analysis. Tirzepatide had a greater decrease in HbA1c, weight loss, lipids, and blood pressure compared with empagliflozin, though there was more uncertainty in these estimates given the indirect comparison. The point estimate decreases in HbA1c and weight loss fell in between the point estimates observed when comparing tirzepatide to injectable semaglutide and comparing tirzepatide to background therapy alone. We did not have data to compare adverse events between tirzepatide and empagliflozin.

Based on data from cardiovascular outcomes trials, semaglutide has an FDA indication for the prevention of cardiovascular events and empagliflozin has FDA indications for the prevention of cardiovascular events and renal disease.<sup>7-9</sup> The cardiovascular outcomes trial for tirzepatide is ongoing; however, data from a cardiovascular safety trial showed a trend towards cardiovascular benefit.

Although tirzepatide shows an impressive impact on glucose-lowering and weight loss, given the established cardiovascular benefits of semaglutide and empagliflozin, establishing whether tirzepatide has similar benefit is imperative to reducing uncertainty in its comparative effectiveness. Additionally, although GLP-1 RAs have longer-term safety and cardiovascular data, the impact of the addition of GIP inhibition is currently unknown. Finally, the lack of head-to-head comparison makes it more difficult to fully assess whether tirzepatide provides superior benefit to empagliflozin.

Thus, compared to background therapy alone, we judge the net health benefits of tirzepatide to be incremental or better (B+). For tirzepatide compared with semaglutide, although tirzepatide had greater impact on glycemic control and weight, the lack of definitive cardiovascular outcomes data causes us to judge tirzepatide to have comparable or incremental net health benefits (C+). For tirzepatide compared with empagliflozin, the indirect comparison and lack of definitive cardiovascular or renal outcomes data, causes more uncertainty about the relative benefit (whether it has comparable, small or even substantial health benefit compared with empagliflozin), and thus we judge tirzepatide to have comparable or better net health benefits (C++).

**Table ES1. Evidence Ratings**

| <b>Treatment</b> | <b>Comparator</b>      | <b>Evidence Rating</b> |
|------------------|------------------------|------------------------|
| Tirzepatide      | Background therapy     | B+                     |
| Tirzepatide      | Injectable Semaglutide | C+                     |
| Tirzepatide      | Empagliflozin          | C++                    |

We developed an individual, patient-level, Monte Carlo-based microsimulation of costs, quality of life, clinical events, and mortality associated with T2DM among US adults using the United Kingdom Prospective Diabetes Study Outcomes Model 2 (UKPDS-OM2)<sup>10</sup> equations. Patients were simulated through the modeling steps for each comparator versus tirzepatide. The base-case analysis took a health care sector perspective and thus focused on direct medical care costs only. All modeled therapies were informed by changes in intermediate outcomes: HbA1c, body weight, low density lipoprotein, and systolic blood pressure. Modeled cardiovascular and renal outcomes for therapies with existing cardiovascular outcomes trials were adjusted to trial data using trial-based hazard ratios. We adjusted tirzepatide’s modeled cardiovascular outcomes based on SURPASS-4 trial’s pooled dosing analysis hazard ratio and its uncertainty. Where possible, we compared the treatment-specific modeled events to that of comparable time horizons from long-term trials.

Tirzepatide had the highest average lifetime discounted quality-adjusted life-years (QALYs) of all considered therapies, however the QALY 95% credible ranges for active comparators overlapped. Equal value of life years (evLY) gained was not reported given no average increased survival when comparing tirzepatide with injectable semaglutide. Using a placeholder price equal to injectable semaglutide, the incremental costs per QALY gained for tirzepatide were around or under \$100,000 versus all comparators with mean differences in health gains and costs being smallest in comparison to injectable semaglutide. Uncertainty analyses suggested a wide range of plausible cost-effectiveness estimates for tirzepatide.

ICER’s Health Benefit Price Benchmarks (HBPBs) are defined as the target prices for a drug that would meet but not surpass benchmarks tied to incremental cost-effectiveness ratios of \$100,000 and \$150,000 per QALY or per evLY gained. Table ES2 illustrates the annual HBPBs for tirzepatide plus background therapy as compared to semaglutide plus background therapy, ranging from an annual price for tirzepatide of \$5,500 to \$5,700. Price reductions or discounts from a list price to reach a HBPB point estimate or range is not applicable for tirzepatide as its list price is currently not available. HBPBs based on evLY gained are not reported given no modeled tirzepatide survival gains versus injectable semaglutide.

**Table ES2. Annual Cost-Effectiveness Health Benefit Price Benchmarks for Tirzepatide**

| Outcome for Annual HBPB Calculation   | Annual WAC | Annual Price at \$100,000 Threshold | Annual Price at \$150,000 Threshold | Discount from WAC to Reach Threshold Prices |
|---|------------|-------------------------------------|-------------------------------------|---|
| Tirzepatide plus Background Therapy vs. Semaglutide plus Background Therapy |            |                                     |                                     |   |
| QALYs Gained  | NA*        | \$5,500                             | \$5,700                             | NA*   |

HBPB: health benefit price benchmark, QALY: quality-adjusted life-year, WAC: wholesale acquisition cost

\*Not applicable (NA) as placeholder prices were used

In summary, tirzepatide improves blood glucose levels and results in weight loss to a greater extent than other diabetes medications. Although early results are promising, definitive data are needed to understand tirzepatide's impact on cardiovascular and renal outcomes. Additionally, because T2DM is more prevalent among minorities, health gains from a successful treatment that has consistent benefits across racial subgroups would provide proportionally greater benefit to those racial groups. Studies have not adequately enrolled minority populations to demonstrate such a consistent effect. Based on current evidence and when compared to injectable semaglutide, the estimated annualized health benefit price benchmark range for tirzepatide is \$5,500 to \$5,700. This range factors in assumptions about long-term cardiovascular benefits that have not yet been directly demonstrated yet in clinical trials. ICER did not issue an Access and Affordability Alert for tirzepatide due to the fact that pricing is not yet known; however, patients and clinicians expressed concern about the overall affordability of T2DM drugs.

Appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, access, and future research are included in the main report. Key policy recommendations are highlighted below.

- All stakeholders have a responsibility to ensure that effective new treatment options for patients with T2DM are introduced in a way that will help reduce health inequities. For example, manufacturers should ensure that the set price for new treatments is in fair alignment with added benefits for patients; payers should ensure that benefit designs do not result in out-of-pocket costs that inappropriately limit access in vulnerable populations; health systems and clinicians should develop programs that prioritize decreasing health inequities in the delivery of diabetes care.
- The prior authorization process should be transparent and not place undue burden on clinicians and patients to ensure timely and equitable access to T2DM medications.
- Given available evidence, it is not unreasonable for payers to consider tirzepatide as part of the GLP-1 RA class or as a separate class for the purposes of coverage.
- Payers should consider removing metformin as step therapy before use of GLP-1 RAs and SGLT-2 inhibitors in certain patients, in line with clinical guidelines. If step therapy is employed, access to both GLP-1 RAs and SGLT-2 inhibitors should be preserved.
- Prices for GLP-1 RAs and SGLT-2 inhibitors are high and coupon programs by manufacturers do not adequately address affordability; development and marketing of generic drugs should not be delayed or denied.
- Especially given the increased burden of T2DM in minority populations, the lack of racial and ethnic diversity in current T2DM clinical trials is unacceptable and future trials should be more reflective of the broader T2DM population.
- More research is needed to generate quality-of-life data and data for use in economic evaluations regarding the societal costs of diabetes.

# 1. Background

---

More than 34 million Americans, or around 13% of the US population, have diabetes mellitus.<sup>1</sup> T2DM, which is characterized by progressive loss of adequate insulin secretion from the pancreas and peripheral resistance to insulin, accounts for 90-95% of those cases. The hallmark of diabetes is an abnormal elevation in blood glucose, or hyperglycemia. Chronic hyperglycemia puts patients at risk for damage to both small (microvascular) and large (macrovascular) blood vessels, resulting in damage to the eyes, nerves, and kidneys, as well as cardiovascular events and limb ischemia.<sup>11</sup> Obesity is a major risk factor for developing T2DM with more than 60% of people with diabetes having a body mass index (BMI) in the obese or extreme obesity range.<sup>1,12</sup> Other risk factors include older age, family history, a history of gestational diabetes, high blood pressure, a sedentary lifestyle, and a low level of HDL.<sup>13</sup>

Minorities bear a disproportionate burden of T2DM. Among adults, the prevalence of diagnosed T2DM is highest in American Indian/Alaska Natives (approximately 14%); for Asian Indian, non-Hispanic Black and Hispanic populations, prevalence estimates are around 12% for each group.<sup>1</sup> These populations are also at greater risk of developing diabetes, with the incidence in Black and Hispanic populations 1.7-1.8 times greater than in White populations.<sup>1,14</sup> Blacks and Hispanics also had lower rates of receipt for HbA1c testing than Whites and were less likely to receive annual cholesterol testing and retinal examination, which may be correlated with higher rates of complications in these populations.<sup>15</sup>

Complications of diabetes can be severe and life-altering. Diabetes is the leading cause of new blindness, end-stage renal disease, and limb amputations, and it is the seventh leading cause of death in the US.<sup>1</sup> In 2016, diabetes was associated with 16 million emergency department visits, 7.8 million hospitalizations, and 1.7 million hospitalizations for cardiovascular disease.<sup>1</sup> Total direct and indirect costs for diabetes exceeded \$327 billion in 2017, with 72% of the total considered direct costs (e.g., health care services or technologies).<sup>2</sup> Furthermore, patients with diabetes are more likely to suffer financial hardship from medical bills and its consequences, including cost-related medication nonadherence, delayed or skipped medical care, high financial distress, and food insecurity.<sup>16</sup>

Management of T2DM is focused on both shorter-term goals such as controlling hyperglycemia and managing comorbidities, and longer-term goals such as preventing complications of disease. Treatment goals are based in part on measurements of HbA1c, a measure of average blood sugar over three months. Since tight control of blood sugar has been shown to decrease microvascular and macrovascular complications, clinical practice guidelines recommend a HbA1c target of 7.0% or less in most patients, with less stringent control accepted in patients with a higher risk of hypoglycemia, more severe comorbidities, and shorter life expectancy.<sup>17</sup> Achieving near-

normal glycemic control with intensive therapy may have additional benefits in terms of slowing onset or progression of neuropathy, retinopathy, and nephropathy.<sup>18</sup> However, such tight control of glucose may come at the expense of more hypoglycemia.

The cornerstones of therapy for T2DM includes lifestyle modifications such as diet, exercise, and weight loss, and management of cardiovascular risk factors such as high cholesterol and high blood pressure.<sup>19,20</sup> Self-management is a critical component of managing diabetes, and individually tailored, culturally appropriate diabetes self-management education can improve outcomes and reduce costs.<sup>21,22</sup> For example, medical nutrition therapy delivered by a registered dietician or diabetic educator is associated with a 0.3-2% decrease in HbA1c in patients with T2DM.<sup>17</sup> For some patients, intensive lifestyle changes may be enough to control blood sugars and prevent progression. However, many patients will require pharmacologic therapy during their disease course to achieve adequate glycemic control.

Metformin is recommended as initial pharmacotherapy for most patients with T2DM due to its efficacy and favorable safety profile and should be continued as long as it is tolerated and not contraindicated.<sup>4</sup> It is associated with modest weight loss, does not have a significant risk of hypoglycemia, and may improve cardiovascular outcomes, though there are no direct cardiovascular outcomes trials.<sup>23</sup> Combination therapy with additional agents can be considered if patients do not meet their HbA1c goal on metformin and lifestyle changes. Older oral medications such as sulfonylureas (SU) and thiazolidinediones (TZD) are inexpensive but have significant side effects such as hypoglycemia (with SU) and heart failure (with TZDs). Newer agents include oral agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors and SGLT-2 inhibitors, and oral and injectable GLP-1 RA. These newer agents are effective at lowering blood glucose without a substantial risk of hypoglycemia, and SGLT-2 inhibitors and GLP-1 RAs are also associated with weight loss, reduction in cardiovascular events, and slowed progression of renal disease. Gastrointestinal side effects are particularly common with GLP-1 RAs and use of SGLT-2 inhibitors are associated with genitourinary infections and ketoacidosis.<sup>24-27</sup>

Since 2008, when the Food and Drug Administration (FDA) issued recommendations for the evaluation of cardiovascular risk for new antihyperglycemic therapies, multiple cardiovascular outcome trials (CVOTs) have been conducted, adding greater certainty in the assessment of the relative risks and benefits of each therapy.<sup>28</sup> Thus, for patients with or at high risk of ASCVD, heart failure, or established chronic kidney disease (CKD) new guidelines recommend that GLP-1 RA or SGLT-2 inhibitor with proven cardiovascular or renal benefit, be considered for first-line therapy, independent of HbA1c target or baseline metformin use.<sup>4</sup> For patients without those comorbidities, choice of drug is dependent on comorbidities, cost, side effects, and patient preferences. More details on each drug class can be found in the [Supplement A2](#).



Although many options for therapy for T2DM exist, nearly half of patients may not be at an adequate level of glycemic control.<sup>1</sup> Tirzepatide (Eli Lilly), a novel, once-weekly injectable dual GIP and GLP-1 receptor agonist, has been developed to treat patients with T2DM. Trials are also ongoing to assess tirzepatide for the treatment of obesity and cardiovascular disease. The manufacturer announced the submission of a biologics license application with priority review to the FDA for T2DM on October 27, 2021, with a decision expected in mid-2022.

**Table 1.1. Intervention of Interest**

| <b>Intervention<br/>(Generic Name)</b> | <b>Mechanism of Action</b>                   | <b>Delivery Route</b>  | <b>Prescribing Information</b> |
|--|--|------------------------|--------------------------------|
| Tirzepatide                            | Dual GIP inhibitor/GLP-1<br>receptor agonist | Subcutaneous injection | 5-15 mg once weekly            |

GIP: glucose-dependent insulinotropic polypeptide, GLP-1: glucagon-like peptide-1, mg: milligrams

## 2. Patient and Caregiver Perspectives

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This evidence report was developed with input from diverse stakeholders, including patients, clinicians, researchers, and manufacturers of the agents of focus in this review.

Patients and patient groups discussed that T2DM has a substantial impact on daily life, including trying to manage diet and blood glucose readings, affording testing supplies and medications, and managing complications of the disease. Patients described the frustrations of trying to follow prescribed diets, particularly when the dietary recommendations conflict (e.g., patients with diabetes are recommended to limit carbohydrates while patients with CKD are recommended to avoid a high protein diet). Glycemic control, particularly HbA1c levels, is one of the most important actionable and short-run outcomes to patients, and patients value potentially getting to near normal glycemic levels.<sup>29</sup> Improvements in glucose tracking with new technologies such as continuous glucose monitors (CGM) are empowering to patients to help manage their daily life and achieve their glycemic goal. Weight loss is another critical struggle described by patients, and patients would welcome medications that would produce significant weight loss. Patients also spoke about feelings of guilt and self-blame for their diabetes, describing the stigma they feel about the perception of diabetes as a “lifestyle” disease that they should be able to control with their actions, even though the causes of diabetes are complex, and genetics can play an important role.

Affordability of diabetes medications and access to CGMs were cited as major barriers to managing T2DM, particularly for patients who are taking medications. Medication costs for patients with diabetes can be substantial, even for those who are insured, and this can affect adherence to medication. For example, co-pays and co-insurance for insulin and newer medications like GLP-1 RAs can be very high, particularly for patients with high deductible health plans, even if they successfully navigate a time-consuming prior authorization process. For patients with lower socioeconomic status, the inability to pay can lead to skipping medication doses and cancelling medical appointments, which may be associated with adverse clinical outcomes.<sup>30</sup> Additionally, patients often have multiple comorbidities such as cardiac or renal disease, which can further increase the financial burden of medications. Patients may turn to foundations or prescription assistance programs from manufacturers to help with medication costs; however, patients with Medicare are usually not eligible for manufacturer prescription assistance programs so such programs have limited reach. Finally, although patients described new technologies such as CGMs as “game changers” in terms of helping them manage their disease, obtaining insurance coverage for CGMs can be very challenging.

Patients discussed that another unmet need is more detailed and comprehensive education about disease management and trajectory, particularly in the time period around diagnosis. In addition, linguistically and culturally sensitive education delivered within the community appears to be a key to improving patient engagement and self-management of the disease. This is particularly

important because the burden of diabetes is substantial in minority populations, with Native Americans/Alaska Natives, Blacks, Hispanics, and Asians having a higher rate of disease compared with White Americans. Thus, patient groups mentioned that a greater focus on efforts to decrease disparities in prevention and treatment of diabetes and accurate modeling of the health effects of diabetes are critical to improving health equity.

Clinicians were enthusiastic about the prospect of therapies that both improved glycemic control and resulted in substantial weight loss. However, they emphasized the importance of cardiovascular outcomes on their assessments of efficacy and were eagerly awaiting the results of the CVOT for tirzepatide. Cost of therapy for patients was an additional issue of great importance to both clinicians and patients and was cited as a major factor in the choice of therapy.

Manufacturers and payers highlighted additional non-glycemic outcomes that may be important to consider when assessing the value of therapy, including improvements in cardiovascular and renal outcomes, satisfaction with the delivery device, and the ability of the therapy to address comorbidities related to obesity that may be impacted by weight loss (e.g., obstructive sleep apnea, nonalcoholic fatty liver disease, etc.).

## 3. Comparative Clinical Effectiveness

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### 3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence of tirzepatide for T2DM are detailed in [Supplement D1](#).

#### Scope of Review

We reviewed the clinical effectiveness of tirzepatide added on to background therapy (metformin +/- sulfonylureas or thiazolidinediones) versus background therapy alone, or injectable semaglutide or empagliflozin added on to background therapy in adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). We sought evidence on patient-important outcomes such as change in HbA1c levels, weight, waist circumference, lipid levels, blood pressure, health-related quality of life measures, and adverse events. Additionally, we reviewed available information on each treatment's effect on micro- and macrovascular outcomes including retinopathy, nephropathy, and neuropathy, all-cause mortality, cardiovascular (CV) mortality, myocardial infarction (MI), stroke, and heart failure requiring hospitalization.

We also looked for data on subpopulations of interest, including T2DM patients with (1) established ASCVD, (2) congestive heart failure, (3) moderate-to-severe renal impairment, (4) requiring a second and/or third antihyperglycemic agent, (5) who are overweight or obese, and (6) identified by race, ethnicity, or socioeconomic status.

The full scope of the review is detailed in [Supplement D1](#).

#### Evidence Base

The SURPASS clinical trial program contains five Phase 3 global registration studies comparing tirzepatide against placebo (background diet and exercise alone), injectable semaglutide, insulin degludec, insulin glargine, and background insulin glargine ± metformin.<sup>31</sup> SURPASS-2 and SURPASS-4 were selected as studies of interest due to a relevant comparator arm or population and are outlined below. We also reviewed two Phase 2 trials to assess the efficacy of tirzepatide added on to background therapy compared with background therapy alone.

### Tirzepatide versus Background Therapy

Our search identified two randomized controlled trials (RCT) of tirzepatide that provide evidence on the efficacy and safety of tirzepatide plus background therapy (diet and exercise alone or with stable metformin treatment) versus background therapy alone. These include a Phase 2b study comparing once-weekly injectable tirzepatide (1, 5, 10, or 15 mg) versus once-weekly injectable dulaglutide (1.5 mg) and placebo (Frias 2018)<sup>5</sup>, and a follow-up Phase 2 study evaluating the tolerability of three tirzepatide dose-escalation regimens (12 mg or two versions of a 15 mg arm) versus placebo (Frias 2020).<sup>32</sup> Participants in both trials were largely on stable metformin doses for background therapy. Baseline characteristics of the two trials are outlined in Table 3.1. The two Phase 2 trials were qualitatively assessed for evidence on the efficacy and safety of tirzepatide as an add-on to background therapy.

**Table 3.1. Selected Baseline Characteristics of Two Phase 2 Tirzepatide Trials**

|                        | Frias 2018 Phase 2 |          |           |           | Frias 2020 Phase 2 |              |              |
|------------------------|--------------------|----------|-----------|-----------|--------------------|--------------|--------------|
| Study Arms             | PBO                | TZP 5 mg | TZP 10 mg | TZP 15 mg | PBO                | TZP 15 mg-1* | TZP 15 mg-2* |
| Background Therapy     | MET                |          |           |           | MET                |              |              |
| Study Duration, weeks  | 26 weeks           |          |           |           | 12 weeks           |              |              |
| Mean Age, years        | 56.6               | 57.9     | 56.5      | 56        | 56                 | 55.5         | 56.6         |
| Sex, Male, %           | 57                 | 62       | 59        | 42        | 46.2               | 57.1         | 82.1         |
| HbA1c, %               | 8                  | 8.2      | 8.2       | 8.1       | 8.2                | 8.5          | 8.4          |
| Weight, kg             | 91.5               | 92.8     | 92.7      | 89.1      | 89.6               | 88.7         | 89.8         |
| BMI, kg/m <sup>2</sup> | 32.4               | 32.9     | 32.6      | 32.2      | 32.5               | 32           | 31.1         |
| Race, White, %         | 80                 | 84       | 74        | 81        | NR                 | NR           | NR           |
| Metformin, %           | 92.2               | 89.1     | 86.3      | 96.2      | 88.5               | 89.3         | 82.1         |

kg: kilogram, m: meter, MET: metformin, mg: milligram, NR: not reported, PBO: placebo, TZP: tirzepatide

\*In the Frias 2020 trial, there were two versions of a 15 mg arm. See [Supplement D3](#) for further details.

Additionally, we conducted a network meta-analysis that provided an indirect comparison of tirzepatide added to background therapy versus background therapy alone using five Phase 3 trials. The NMA is described in further detail in the evidence base for the tirzepatide versus empagliflozin scenario and in [Supplement D2](#).

### Tirzepatide versus Semaglutide

SURPASS-2 is a Phase 3 head-to-head open-label trial evaluating the clinical efficacy and safety of tirzepatide (5, 10, or 15 mg) versus injectable semaglutide (1 mg) over a 40-week period in patients with T2DM inadequately controlled with baseline metformin therapy. Baseline characteristics can be found in Table 3.2, and additional details of the study design can be found in [Supplemental Table D4.3](#).

## Tirzepatide versus Empagliflozin

There are no head-to-head trials comparing the clinical efficacy and safety of tirzepatide versus empagliflozin. Thus, to be able to draw an indirect comparison between the two treatments, we conducted a NMA on the available intermediate outcomes of changes in HbA1c, weight, low-density lipoprotein (LDL) cholesterol, and systolic blood pressure (SBP). These outcomes were presented as between-treatment mean differences of change from baseline at 40 weeks. We included five Phase 3 trials and five drugs into the network: tirzepatide (SURPASS-2), injectable semaglutide (SURPASS-2, SUSTAIN-2), oral semaglutide (PIONEER-2, PIONEER-3), empagliflozin (PIONEER-2), and sitagliptin (SUSTAIN-2, PIONEER-3, HARMONY-3) ([Figure D2.1](#)). The study design and baseline characteristics of the five trials are outlined in Table 3.2.

**Table 3.2. Selected Study Design and Baseline Characteristics of the Randomized Controlled Trials in the Network Meta-Analysis Evaluating Tirzepatide, Semaglutide, Empagliflozin, and Background Therapy**

|                        | SURPASS-2    |             | SUSTAIN-2        |                | PIONEER-2     |               | PIONEER-3        |                | HARMONY-3 |                |
|------------------------|--------------|-------------|------------------|----------------|---------------|---------------|------------------|----------------|-----------|----------------|
| Study Arms             | TZP<br>15 mg | SEM<br>1 mg | SEM<br>1 mg      | SITA<br>100 mg | OSEM<br>14 mg | EMPA<br>25 mg | OSEM<br>14 mg    | SITA<br>100 mg | PBO       | SITA<br>100 mg |
| N                      | 470          | 469         | 409              | 407            | 411           | 410           | 465              | 467            | 101       | 302            |
| Background Therapy     | MET          |             | MET ± TZD (4.5%) |                | MET           |               | MET ± SU (47.1%) |                | MET       |                |
| Study Duration         | 40 weeks     |             | 56 weeks         |                | 52 weeks      |               | 78 weeks         |                | 104 weeks |                |
| Mean Age, years        | 55.9         | 56.9        | 56               | 54.6           | 57            | 58            | 57               | 58             | 56.1      | 54.3           |
| Sex, Male, %           | 45.5         | 48          | 50               | 51             | 50.1          | 51            | 53.1             | 51.0           | 49.5      | 46             |
| HbA1c, %               | 8.3          | 8.3         | 8                | 8.2            | 8.1           | 8.1           | 8.3              | 8.3            | 8.2       | 8.1            |
| Weight, kg             | 93.8         | 93.7        | 89.2             | 89.3           | 91.9          | 91.3          | 91.2             | 90.9           | 91.6      | 90.3           |
| BMI, kg/m <sup>2</sup> | 34.5         | 34.2        | 32.5             | 32.5           | 32.9          | 32.8          | 32.3             | 32.5           | 32.8      | 32.5           |
| Race, White, %         | 71.1         | 71.6        | 68               | 69             | 86.4          | 86.1          | 68.2             | 71.3           | 63.4      | 74.5           |
| Metformin, %           | 100          | 100         | 100              | 100            | 100           | 100           | 100              | 100            | 100       | 100            |

EMPA: empagliflozin, kg: kilogram, m: meter, MET: metformin, N: number of subjects in full analysis set, OSEM: oral semaglutide, PBO: placebo/background therapy, SEM: injectable semaglutide, SITA: sitagliptin, SU: sulfonylurea, TZD: thiazolidinediones, TZP: tirzepatide

## Cardiovascular Outcomes Trials

### Tirzepatide

The SURPASS-CVOT is evaluating the non-inferiority and superiority of once weekly tirzepatide versus dulaglutide (1.5 mg) in participants with T2DM and increased cardiovascular risk.<sup>33</sup> The trial has an estimated completion date of October 17, 2024; interim data was unavailable at the time of this report.<sup>33</sup>

In lieu of SURPASS-CVOT data, we sought data on baseline characteristics, efficacy, and adverse event parameters of SURPASS-4, a Phase 3 trial that evaluated three doses of tirzepatide (5, 10, 15

mg) against insulin glargine in adults with T2DM on 1-3 oral antihyperglycemic medications and increased cardiovascular risk.<sup>34</sup> Cardiovascular events were recorded as safety events. Additional details of the trial are available in [Supplemental Table D4.2](#).

Due to the unavailability of long-term CVOT data and lack of placebo arm in the above tirzepatide trials, we were unable to include any microvascular (neuropathy, nephropathy, and retinopathy) or macrovascular outcomes (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina or heart failure) in our NMA.

#### Injectable Semaglutide

SUSTAIN-6 was a CVOT that assessed the efficacy and safety of semaglutide (0.5 or 1 mg) versus placebo as an add-on therapy to background therapy (73.2% on metformin, 58% on insulin, 42.8% on sulfonylurea) in patients with T2DM and established ASCVD, CKD, or both.<sup>7</sup> A total of 3297 patients with a mean age of 64.6 years and baseline HbA1c of 8.7% were observed for a median period of 2.1 years.<sup>7</sup> The pooled semaglutide group was analyzed for non-inferiority and superiority versus the placebo group for the primary composite outcome of MACE-3 (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke).<sup>7</sup> Additional details of the trial are available in [Supplemental Table D4.2](#).

#### Empagliflozin

EMPA-REG OUTCOME was a CVOT that assessed the efficacy and safety of empagliflozin (10 or 25 mg) as an add-on to background therapy (74% on metformin, 48% on insulin, 43% on sulfonylurea) in patients with T2DM and established cardiovascular disease.<sup>8,35</sup> In this trial, 7020 patients with a mean age of 63.1 years and a baseline HbA1c of 8.1% were treated and observed for a median period of 2.6 and 3.1 years, respectively.<sup>8</sup> The pooled empagliflozin group was analyzed for non-inferiority and superiority versus the placebo group for the primary composite outcome of MACE-3 (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and the key secondary composite outcome of MACE-3 or hospitalization for unstable angina.<sup>8</sup> Additional details of the trial are available in [Supplemental Table D4.2](#).

### Subgroup Analysis of Patient-Important Outcomes

Our population of interest for this review are adults with T2DM with inadequate glycemic control despite current treatment with background therapy. In addition to our primary analysis, we sought to evaluate all available patient-important outcomes in the context of the following six patient subgroups:

1. Established ASCVD, e.g., a history of acute coronary syndrome (ACS), MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease.<sup>36</sup>

Currently, there is no available evidence to evaluate the clinical efficacy or safety of tirzepatide for this subgroup. The SURPASS-4 trial included participants with an increased risk of ASCVD as well as participants with established ASCVD; cardiovascular events were recorded as safety events.<sup>34</sup> When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

2. Established congestive heart failure (New York Heart Association class II or III)

Currently, there is no available evidence to evaluate the clinical efficacy and safety of tirzepatide for this subgroup. When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

3. Established moderate-to-severe renal impairment (CKD Stage 3 or higher (eGFR <60 mL/min per 1.73 m<sup>2</sup>))

Academic-in-confidence data on change in HbA1c (%) from baseline at week 40 between the subgroups of eGFR <60 and ≥60 mL/min per 1.73 m<sup>2</sup> for the SURPASS-2 trial was provided by the manufacturer.<sup>37</sup> When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

4. Tirzepatide as a second- or third-line antihyperglycemic agent

We did not find any data assessing the efficacy or safety of tirzepatide specific to these two subpopulations. When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

5. Overweight (BMI 25.0-29.9 kg/m<sup>2</sup>) or obese (≥30.0 kg/m<sup>2</sup>)

Academic-in-confidence data on change in HbA1c (%) from baseline at week 40 between the subgroups of BMI <30 kg/m<sup>2</sup>, ≥30 to <35 kg/m<sup>2</sup>, and ≥35 kg/m<sup>2</sup> was provided by the manufacturer for the SURPASS-2 trial.<sup>37</sup> When available, we qualitatively assessed any subgroup analyses done in these populations in the semaglutide and empagliflozin CVOTs.



## 6. Race and ethnicity or socioeconomic status

Academic-in-confidence data on change in HbA1c (%) from baseline at week 40 between the subgroups of Hispanic/Latino and Not Hispanic/Latino was provided by the manufacturer for the SURPASS-2 trial.<sup>37</sup> When available, we qualitatively assessed any subgroup analyses done in this population in the semaglutide and empagliflozin CVOTs.

## 3.2. Results

A subset of trials within our review report treatment effects using two estimands. The treatment-regimen, also called treatment policy, estimand evaluates the treatment effect for all randomized patients regardless of premature trial product discontinuation or use of rescue medication.<sup>6,38</sup> The efficacy, or trial product, estimand evaluates the treatment effect of all randomized patients who had completed the study without the use of rescue medication. The treatment-regimen estimand and the efficacy estimand provide different perspectives on a drug's efficacy; we feel that the treatment-regimen/treatment policy estimand is more relevant to the patient and clinician experience as it considers the common challenges of medication adherence and need for rescue medication in the diabetes treatment realm.

When possible, we prioritized the reporting of values from the treatment-regimen estimand for several reasons: to ensure consistency with our 2019 ICER Type 2 Diabetes report, the estimand's reflection of the intention-to-treat principle, and its preference by regulatory agencies such as the FDA.<sup>39</sup> If the treatment-regimen estimand was not available, we reported efficacy estimands and have noted as such via in-text and evidence table references.

We conducted an NMA comparing tirzepatide added to background therapy to background therapy alone, and injectable semaglutide or empagliflozin added to background therapy. Oral semaglutide and sitagliptin were used as linkages in the NMA and therefore were not emphasized in this report. Additionally, due to limited data reported in publications and/or provided by manufacturers, there were only four available outcomes for which we could provide inputs into the NMA: change from baseline in HbA1c, body weight, LDL, and SBP at week 40. ([Supplemental Tables D2.2-2.3](#))

## Clinical Benefits

### *Tirzepatide versus Background Therapy*

The efficacy of tirzepatide compared with background therapy was evaluated through two Phase 2 trials (Frias 2018 and Frias 2020) and the NMA. Tirzepatide consistently showed a dose-dependent decrease in HbA1c of -1.6% to -2.4% compared with background therapy (efficacy estimand). Results from the NMA were consistent with these trials, with an estimated treatment difference in HbA1c from placebo of -1.7%. Furthermore, in the Frias 2018 trial, all three tirzepatide doses had a

greater proportion of participants who achieved a HbA1c target of <7.0% (69.1-90.0%) compared to placebo (11.8%) ( $p<.0001$  for all three comparisons), and 30.2% of participants in the tirzepatide 15 mg arm achieved HbA1c levels of <5.7%, an indication of normal glycemic control. ([Supplement Table D4.4](#))

In terms of weight, tirzepatide also showed a dose-dependent decrease in weight ([Supplement Table D4.4](#)), with the greatest weight loss seen in the tirzepatide 15 mg group (-11.3 kg from baseline in the Frias 2018 trial and -9.51 kg difference from placebo in the NMA). Additionally, in the Frias 2018 trial, more than one-third of patients in the 10 mg and 15 mg groups achieved body weight reduction of  $\geq 10\%$  and almost one-quarter of participants in the 15 mg arm achieved  $\geq 15\%$  reduction. Impact on waist circumference was mixed between the two trials. ([Supplement Table D4.4](#))

The impact of tirzepatide on other outcomes was mixed. Tirzepatide had a statistically significant decrease of 7.46 mmHg in systolic blood pressure compared with placebo in the NMA (random effects model) but not the Phase 2 trials. Similarly, tirzepatide had a statistically significant decrease in LDL of 4.33 mg/dL from baseline in the NMA (random effects model) that was not seen in the Phase 2 trials. Tirzepatide also decreased mean total cholesterol and triglycerides concentrations ( $p<.05$  for all interactions) in the Frias 2018 trial ([Supplement Table D4.4](#)).

#### *Tirzepatide versus Semaglutide*

The primary outcome of the SURPASS-2 trial was the mean change in HbA1c from baseline to 40 weeks between three arms of tirzepatide (5 mg, 10 mg, or 15mg) and injectable semaglutide (1 mg). Tirzepatide reduced HbA1c levels by 2%, 2.2%, and 2.3% in the 5 mg, 10 mg, and 15 mg dose groups, respectively, compared with 1.86% with semaglutide. The estimated treatment differences for all groups compared with semaglutide were statistically significant: tirzepatide 5 mg -0.15% (95% CI -0.28 to -0.03); tirzepatide 10 mg -0.39% (-0.51 to -0.26); tirzepatide 15 mg -0.45% (-0.57 to -0.32).

Additionally, the two larger tirzepatide doses (10 mg, 15 mg) also had a greater proportion of participants who achieved a HbA1c target of <7.0% (86%) compared to semaglutide (79%) ( $p<.05$  for both dose groups). Nearly half of participants in the tirzepatide 10 mg and 15 mg arms achieved near-normal glucose levels (HbA1c <5.7%), compared with 19% in the semaglutide arm ( $p<.001$ ).

Treatment with tirzepatide produced a dose-dependent change in mean body weight (kg) from baseline compared with semaglutide. At week 40, participants experienced a weight loss of 7.6 kg (5 mg), 9.3 kg (10 mg), and 11.2 kg (15 mg) compared with 5.7 kg in the semaglutide group ( $p<.0001$  for all three comparisons). The percentage of participants achieving body weight reduction of  $\geq 10\%$  was 24% (semaglutide), 34% (5 mg), 47% (10 mg), and 57% (15 mg), and 36% of participants in the 15 mg arm achieved a  $\geq 15\%$  reduction in body weight. Finally, at week 40, there was a greater

reduction in mean waist circumference (cm) in all three dosage arms of tirzepatide compared with semaglutide ([Supplement Table D4.5](#)).

The 15 mg tirzepatide arm had a greater reduction in systolic and diastolic blood pressure from baseline (–6.5 mmHg and –2.9 mmHg, respectively) as compared with 1 mg semaglutide (–3.6 mmHg and –1.0 mmHg, respectively). Treatment with tirzepatide also resulted in a greater increase in mean HDL and a greater reduction in triglycerides concentrations versus semaglutide across the three dosage arms (efficacy estimand) ([Supplement Table D4.5](#)). Changes in mean total cholesterol and LDL concentrations were not statistically significant among the four treatment groups (efficacy estimand).

Treatment with 15 mg of tirzepatide resulted in numerically better overall quality of life compared with semaglutide across several quality-of-life measures, including the Diabetes Treatment Satisfaction Questionnaire change version (DTSQc), EQ-5D-5L (index score), EQ-5D-5L visual analogue scale (VAS), Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) (psychosocial, physical, and physical functioning score).<sup>40</sup>

#### *Tirzepatide versus Empagliflozin*

As there are no head-to-head trials comparing tirzepatide to empagliflozin, all results for this comparison are derived from the NMA. Compared with empagliflozin, tirzepatide decreased HbA1c by 1.1% (statistically significant change using random effects model) ([Supplemental Table D2.4](#)). A similar advantage is seen in the comparison of weight loss, with an estimated mean difference of –7.2 kg between tirzepatide and empagliflozin (statistically significant change using random effects model) ([Supplemental Table D2.4](#)).

Tirzepatide appears to decrease systolic blood pressure by 2.6 mmHg compared with empagliflozin (statistically significant change using random effects model) ([Supplemental Table D2.4](#)). For the outcome of LDL, tirzepatide appears to lower LDL by 7.5 mg/dL compared with empagliflozin (statistically significant change using random effects model) (efficacy estimand)([Supplemental Table D2.4](#)).

#### *Cardiovascular Outcomes*

##### *Tirzepatide*

Although the CVOT for tirzepatide is ongoing, the manufacturer performed a CV safety meta-analysis within SURPASS-4 and across the five SURPASS trials on the adjudicated composite outcome (MACE-4) of death from cardiovascular or undetermined causes, myocardial infarction, stroke, and hospitalization for unstable angina. In SURPASS-4, there was no evidence of an increase in the occurrence of MACE-4 and there was an overall trend towards benefit (HR: 0.74; 95% CI: 0.51 to 1.08; p=NR).<sup>34</sup> Additionally, the tirzepatide 15 mg group showed a decrease in MACE-4 (HR 0.50;

95% CI 0.26-0.95) over a median of 85 weeks of follow-up.<sup>34</sup> Likewise, pooled data from the SURPASS program showed that tirzepatide had a trend towards benefit in the occurrence of MACE-4 as compared to pooled comparators (HR: 0.81; 97.85% CI: 0.52 to 1.26; p=NR).<sup>41</sup>

### Injectable Semaglutide

The primary outcome of the SUSTAIN-6 CVOT was the first occurrence of MACE-3 (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The pooled doses of semaglutide (0.5 mg and 1 mg) were noninferior and superior to placebo in reducing the occurrence of MACE-3 (HR: 0.74; 95% CI: 0.58 to 0.95; p<0.001 for noninferiority; p=0.02 for superiority). When expanding the primary composite outcome to also include the occurrences of revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure, semaglutide was noninferior to placebo (HR: 0.74; 95% CI: 0.62 to 0.89; p=.002). The reduction of risk in both composite outcomes was largely driven by semaglutide's ability to reduce the occurrence of nonfatal stroke versus placebo (HR: 0.61; 0.38 to 0.99; p<.04); the differences in risk reduction between semaglutide and placebo were not statistically significant for the remaining components of the composite outcomes: cardiovascular or all-cause death, nonfatal MI, hospitalization for unstable angina or heart failure ([Supplemental Table D4.10](#)).

SUSTAIN-6 included several pre-specified subgroup analyses of interest for the primary outcome of MACE-3: established cardiovascular disease, established chronic heart failure, established moderate-to-severe renal impairment, baseline BMI, race, and ethnicity. None of the subgroups had a statistically significant treatment interaction between semaglutide and placebo ([Supplemental Table D4.11](#)).

There was mixed evidence on semaglutide's impact on microvascular outcomes. When compared to placebo, semaglutide reduced the risk of new or worsening nephropathy (HR, 0.64; 95% CI: 0.46 to 0.88; p=.005) but was associated with an increased the risk of diabetic retinopathy complications (HR: 1.76; 95% CI: 1.11 to 2.78; p=.02), although it is not clear whether semaglutide's effect on retinopathy differs between patients with and without baseline retinopathy.<sup>42</sup> The incidence of diabetic neuropathy was not reported in SUSTAIN-6.

Data from the SUSTAIN-6 CVOT led to semaglutide's approved indication of reducing the risk of cardiovascular death, nonfatal MI, or nonfatal stroke in adults with T2DM and established cardiovascular disease.<sup>43</sup>

### Empagliflozin

The primary outcome of the EMPA-REG OUTCOME CVOT was the first occurrence of MACE-3. The pooled doses of empagliflozin (10 mg and 25 mg) were noninferior and superior to placebo in reducing the occurrence of MACE-3 (HR: 0.86; 95% CI: 0.74 to 0.99; p<0.001 for noninferiority; p=0.04 for superiority). When expanding the primary composite outcome to also include

hospitalization for unstable angina, empagliflozin was noninferior but not superior to placebo (HR: 0.89; 95% CI: 0.78 to 1.01;  $p < 0.001$  for noninferiority;  $p = 0.08$  for superiority).

The reduction of risk in both composite outcomes was largely driven by empagliflozin's ability to reduce the occurrence of cardiovascular death by 38% (HR: 0.62; 0.49 to 0.77;  $p < .001$ ); the differences in risk reduction between empagliflozin and placebo were not statistically significant for the remaining components of the composite outcomes ([Supplemental Table D4.10](#)). Patients in the empagliflozin group also had lower risk than placebo from hospitalization for heart failure and death from any cause ([Supplemental Table D4.10](#)).

EMPA-REG OUTCOME included several pre-specified subgroup analyses of interest for the outcomes of MACE-3 and cardiovascular death: established moderate-to-severe renal impairment, baseline BMI, race, and ethnicity (CV death only). For MACE-3, none of the subgroups had a statistically significant treatment interaction between empagliflozin and placebo ([Supplemental Table D4.11](#)).

There was mixed evidence on empagliflozin's impact on microvascular outcomes. There was a statistically significant difference between the empagliflozin and placebo group on the reduced risk of new or worsening nephropathy (HR, 0.61; 95% CI: 0.53 to 0.70;  $p < .001$ ) but not the risk of diabetic retinopathy complications (HR: 0.69; 95% CI: 0.43 to 1.12;  $p = .134$ ). The incidence of diabetic neuropathy was not reported in EMPA-REG OUTCOME.

Data from the EMPA-REG OUTCOME CVOT led to empagliflozin's approval for the indication of reducing the risk of cardiovascular death in adults with T2DM and established cardiovascular disease.<sup>44</sup>

Participants treated with empagliflozin in the EMPA-REG OUTCOME CVOT group experienced statistically significantly lower rates of both acute renal failure ( $p < .01$ ) and acute kidney injury ( $p < .05$ ) than placebo, suggesting a renal protective effect. These promising results have led to further study of empagliflozin's effect on kidney disease progression or CV death in adults with established chronic kidney disease both with and without diabetes (EMPA-KIDNEY), scheduled to conclude in 2022.<sup>45</sup>

**Table 3.3. CVOT Key Trial Results**

| Cardiovascular Outcomes    |              | SUSTAIN-6           |            | EMPA-REG OUTCOME    |                 |
|----------------------------|--------------|---------------------|------------|---------------------|-----------------|
|                            |              | SEM 1 mg            | PBO 1 mg   | PBO                 | EMPA (10/25 mg) |
| Composite Outcome          | n (%)        | 108 (6.6)           | 146 (8.9)  | 282 (12.1)          | 490 (10.5)      |
|                            | HR (95%CI)   | 0.74 (0.58 to 0.95) |            | 0.86 (0.74 to 0.99) |                 |
|                            | p-value, NON | <0.001              | REF        | <.001               | REF             |
|                            | p-value, SUP | 0.02                | REF        | 0.04                | REF             |
| Expanded Composite Outcome | n (%)        | 199 (12.1)          | 264 (16.0) | 333 (14.3)          | 599 (12.8)      |
|                            | HR (95%CI)   | 0.74 (0.62 to 0.89) |            | 0.89 (0.78 to 1.01) |                 |
|                            | p-value, NON | 0.002               | REF        | <.001               | REF             |
|                            | p-value, SUP | NA                  | NA         | 0.08                | REF             |

CI: confidence interval, EMPA: empagliflozin, HR: hazard ratio, n: number, NA: not applicable, NON: noninferiority, PBO: placebo, REF: reference, SEM: injectable semaglutide, SUP: superiority

## Harms

### Tirzepatide versus Background Therapy

The most frequent adverse events in the Frias 2018 and 2020 trials for tirzepatide compared with background therapy were gastrointestinal-related. Participants in the tirzepatide 15 mg arm experienced nausea (40%), diarrhea (32%), or vomiting (26%) at greater proportion than placebo ([Supplemental Table D4.6](#)). The discontinuation rate in the 15 mg arm was substantial in the Frias 2018 study (24.5% vs. 3.9% placebo).

Other adverse events in the two trials included hypoglycemia (plasma glucose of  $\leq 70$  mg/dL) (10-18%), decreased appetite (18-28%), headache (9-21%), abdominal pain (5-18%), dizziness (9-11%), and injection site reaction (6-8%). There were no reported episodes of severe hypoglycemia across the two trials.

### Tirzepatide versus Semaglutide

The safety profile of tirzepatide in the 40 week SURPASS-2 trial was consistent with Phase 2 results; the most frequent adverse events were gastrointestinal-related ([Supplemental Table D4.6](#)). A greater proportion of participants in the tirzepatide 15 mg arm had a serious adverse event than in the semaglutide arm (5.7% vs. 2.8%). Adverse events resulted in the discontinuation of the active treatment in 8.5% (15 mg tirzepatide) and 4.1% (1 mg semaglutide) of participants.

Injection-site reactions (4.5% vs. 0.2%) and hypoglycemia (1.7% vs. 0.4%) were more frequent in the tirzepatide 15 mg arm compared with semaglutide. Both drugs had similar rates of adjudicated pancreatitis, hypersensitivity, and cholelithiasis ([Supplemental Table D4.6](#)). There were no cases of

diabetic retinopathy among the 15 mg tirzepatide or 1 mg semaglutide arms, with two cases (0.4%) in the 10 mg tirzepatide arm.

#### *Tirzepatide versus Empagliflozin*

There were no available direct or indirect comparisons of safety outcomes between tirzepatide and empagliflozin.

### **Subgroup Analyses and Heterogeneity**

#### *Established ASCVD*

Currently, there is no available evidence to evaluate the clinical efficacy and safety of tirzepatide for this subgroup. The SUSTAIN CVOT trial is ongoing and expected to be completed in 2024.

#### *Established CHF*

Currently, there is no available evidence to evaluate the clinical efficacy and safety of tirzepatide for this subgroup.

#### *Established moderate-to-severe renal impairment*

In the 40 week SURPASS-2 trial, participants receiving tirzepatide 15 mg achieved a greater reduction in HbA1c from baseline than semaglutide, irrespective of renal impairment (eGFR <60, ≥60 mL/min per 1.73 m<sup>2</sup>).<sup>37</sup>(data on file) Participants with established moderate-to-severe renal impairment (eGFR <60 mL/min per 1.73 m<sup>2</sup>) experienced a smaller reduction in HbA1c from baseline in both trial arms.<sup>37</sup>(data on file)

#### *Obesity*

In the 40 week SURPASS-2 trial, participants receiving tirzepatide 15 mg achieved a greater reduction in HbA1c from baseline than semaglutide, irrespective of obesity status (BMI categories <30 kg/m<sup>2</sup>, ≥30 to <35 kg/m<sup>2</sup>, ≥35 kg/m<sup>2</sup>).<sup>37</sup>(data on file)

#### *Race and ethnicity or socioeconomic status*

In the 40 week SURPASS-2 trial, Hispanic/Latino participants experienced a greater reduction in HbA1c from baseline in all trial arms compared with non-Hispanic/Latino participants, with the pattern of relative HbA1c decline between groups consistent with the overall trial results (i.e., greater reduction in HbA1c in the tirzepatide arms compared with semaglutide) <sup>37</sup> (data on file)



## Heterogeneity

Table 3.2 outlines the baseline characteristics across the five trials used in our NMA. There were no notable differences between studies in the distribution of baseline characteristics of age, sex, race, ethnicity, HbA1c, weight, BMI, and background use of metformin. We were unable to assess baseline history of microvascular or macrovascular events. Participants in the SUSTAIN-2 and PIONEER-3 trials received additional background therapy via thiazolidinediones and sulfonylurea, respectively.

## **Uncertainty and Controversies**

For the newer antihyperglycemic drugs, particularly GLP-1 RAs and SGLT-2 inhibitors, the glucose-lowering effect of the drug is only one facet of its overall clinical value. The importance of other outcomes such as weight loss, prevention of cardiovascular events, and renal protection have gained prominence, as reflected both by separate indications for such benefits and in clinical practice guidelines suggesting that GLP-1 RAs and SGLT-2 inhibitors be considered as first-line drug therapy for certain groups of patients with T2DM, regardless of HbA1c level and baseline metformin use.<sup>4</sup> Thus, the value assessment of new T2DM therapies includes examining data beyond glucose lowering and glycemic control.

Tirzepatide shows an impressive impact on glucose-lowering and glycemic control, with an average HbA1c lowering of around 2% compared with background therapy, 0.45% in direct comparison to semaglutide and 1.1% in indirect comparison to empagliflozin. Additionally, a substantial number of patients taking 15 mg of tirzepatide achieved near-normal glycemic levels, which is both important to patients and may have benefits in terms of slowing progression of disease.<sup>18</sup>

Tirzepatide is also associated with more weight loss than its comparators. Given that the majority of patients with T2DM are overweight or obese and that nearly half of patients with T2DM are inadequately controlled on current therapy, these results are promising. However, gastrointestinal side effects were frequent with tirzepatide, and this may affect real-world acceptance and adherence of the drug. Furthermore, GLP-1 RAs may be associated with an increased risk of pancreatitis, acute kidney injury, and thyroid cancer, and GIP inhibition is a new mechanism of action so long-term side effects of this type of drug are unknown.<sup>46</sup> Finally, the durability of tirzepatide's effect on glycemic control and other parameters such as weight loss, are not yet known. Since there are already multiple effective options for treatment of T2DM, the unknown harms of tirzepatide may influence treatment decision-making by clinicians and patients.

The data on cardiovascular and renal outcomes for tirzepatide is currently immature, and thus it is not yet clear whether tirzepatide improves cardiovascular and renal outcomes, as has been demonstrated by its comparators. It is reassuring that tirzepatide did not show any cardiovascular harm in a safety meta-analysis across the SURPASS trials and encouraging that it had a greater impact on surrogate cardiovascular outcomes such as blood pressure and lipids in comparison to



semaglutide and empagliflozin and a trend towards cardiovascular benefit overall in SURPASS-4. However, SURPASS-4 was only powered to demonstrate cardiovascular safety, and the formal CVOT to provide more definitive data on cardiovascular outcomes is ongoing. Additionally, although GLP-1 receptor agonism is part of the mechanism for tirzepatide, the drug has an additional mechanism of GIP inhibition, which may have some direct effects in the myocardium. There are mixed data from pre-clinical, clinical, and epidemiological studies on whether GIP inhibition is helpful or harmful with regard to protection from cardiovascular events.<sup>47-50</sup> Finally, cardiovascular benefit is not uniform across the GLP-1 RA class.<sup>51</sup> Therefore, we hesitate to fully extrapolate the cardiovascular benefits of GLP-1 RAs like semaglutide to tirzepatide, and eagerly await the results from tirzepatide's CVOT.

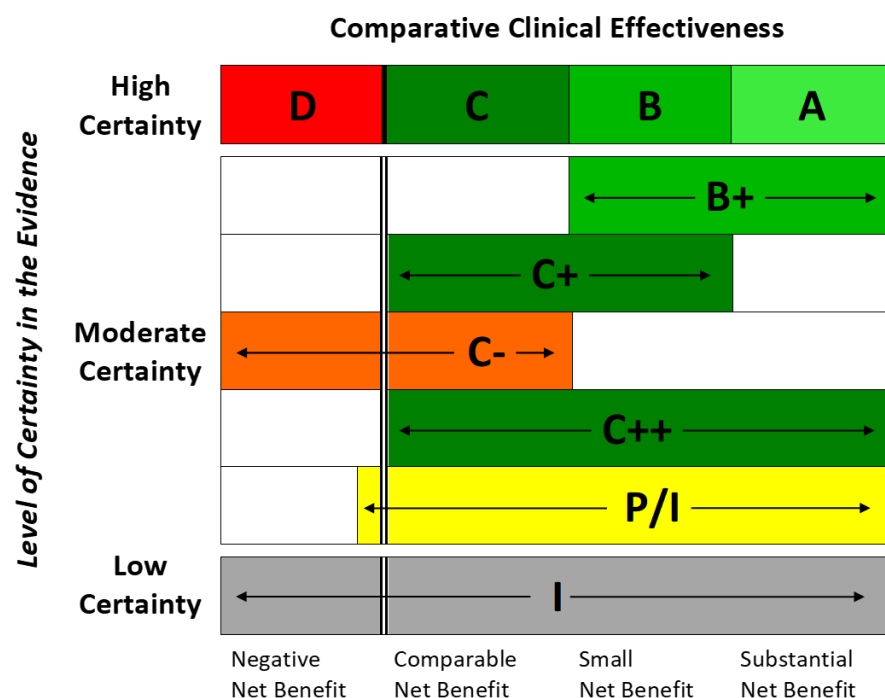
The lack of head-to-head comparison between tirzepatide and empagliflozin made our assessment of the net benefit of tirzepatide more challenging. Since tirzepatide and empagliflozin have completely different mechanisms of action, without a direct comparison, it is difficult to judge whether tirzepatide may represent a substantial improvement over empagliflozin, particularly in patients with established or at high risk of ASCVD, CKD, or heart failure; three common comorbid conditions. However, tirzepatide did show statistically significant and likely clinically significant improvements in HbA1c, weight loss, SBP and lipid parameters, though we have only moderate certainty about the results from the indirect comparison through the NMA.

Finally, T2DM is a disease that disproportionately affects minority populations. However, trials of antihyperglycemic drugs including tirzepatide do not reflect the demographics of the disease in the US. The lack of inclusion of minority populations in the clinical trials poses a serious issue in terms of evaluating whether new treatments may increase or decrease health inequities. Furthermore, as access to newer, potentially more expensive drugs tends to be limited at least during initial launch, missing potential differences in population subgroups may prevent populations who may derive greater benefit from the drug from being able to access it. More diverse representation in clinical trials can also provide more precise data to help match drugs with the patients who have the most favorable benefit/side effect profile, which may in turn improve adherence and clinical outcomes of treatment.

### 3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided in the Supplement ([Section D](#)).

Figure 3.1. ICER Evidence Rating Matrix



**A = "Superior"** - High certainty of a substantial (moderate-large) net health benefit  
**B = "Incremental"** - High certainty of a small net health benefit  
**C = "Comparable"** - High certainty of a comparable net health benefit  
**D = "Negative"** - High certainty of an inferior net health benefit  
**B+ = "Incremental or Better"** - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit  
**C+ = "Comparable or Incremental"** - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit  
**C- = "Comparable or Inferior"** - Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit  
**C++ = "Comparable or Better"** - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit  
**P/I = "Promising but Inconclusive"** - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit  
**I = "Insufficient"** - Any situation in which the level of certainty in the evidence is low

In this review, we set out to compare the clinical efficacy and safety of tirzepatide to background therapy, injectable semaglutide and empagliflozin.

For the comparison between tirzepatide and background therapy, we evaluated data from two Phase 2 trials on change in glucose levels, weight, lipid profiles, and blood pressure, as well as indirect comparisons on glycemic control, weight loss, LDL, and SBP via results from a five trial

NMA. Compared to background therapy, tirzepatide treatment provided consistent, substantial, and clinically meaningful reductions in HbA1c and weight across the two trials; results for systolic blood pressure and LDL are more modest. The NMA results support the superiority of tirzepatide over background therapy, with statistically significant treatment differences in HbA1c, weight, LDL and SBP. The impact of tirzepatide on cardiovascular outcomes has yet to be determined; however, SURPASS-4 provides a glimpse into the positive direction of tirzepatide's cardiovascular safety and potential benefit (in comparison with insulin). Finally, although there was a relatively high discontinuation rate due to gastrointestinal side effects seen in the Phase 2 trial, dose titration appears to mitigate these effects, and severe adverse events are rare. Therefore, we have high certainty that tirzepatide provides a substantial net benefit compared with background therapy for glycemic control and weight loss. We judge tirzepatide to be incremental or better ("B+") for this comparison.

For the comparison between tirzepatide and injectable semaglutide, we relied on head-to-head evidence from a Phase 3 trial (SURPASS-2) to evaluate change from baseline in the intermediate outcomes of glucose levels, weight, lipid profiles, blood pressure, and quality-of-life. Tirzepatide demonstrated a small estimated net benefit in reducing HbA1c and substantial net benefit in weight loss when compared to semaglutide. The drugs appear to be comparable in terms of effects on lipid profile and blood pressure. However, while semaglutide has been demonstrated to improve cardiovascular outcomes and has an indication for this purpose, these data are currently lacking for tirzepatide. We hesitate to fully extrapolate the favorable cardiovascular outcomes data for GLP-1 RAs to tirzepatide, as cardiovascular benefit is not uniform across the GLP-1 RA class, and because of the dual GLP-1/GIP mechanism of action. In consideration of tirzepatide's superiority over semaglutide in outcomes of glycemic control and weight loss, similar safety profiles but current lack of definitive cardiovascular outcome data and the uncertainty about the impact of the GIP moiety, we judge tirzepatide to be comparable or incremental ("C+") for this comparison, with a high certainty of at least a comparable net benefit.

For the comparison between tirzepatide and empagliflozin, tirzepatide provided a substantial net benefit versus empagliflozin via changes in HbA1c, weight, LDL, and SBP. However, with no direct head-to-head trials, we were limited to making an indirect comparison via NMA and thus there is more uncertainty in the precision of these estimates. Additionally, empagliflozin has established cardiovascular and renal benefits in adults with T2DM; data on such outcomes is less certain for tirzepatide, though early signals for the cardiovascular benefit of the drug are promising. Thus, tirzepatide may provide anywhere from comparable net health benefits (if tirzepatide shows equivalent cardiovascular and renal benefits to empagliflozin) to substantial net health benefits (if the improvements in intermediate outcomes over empagliflozin translate into larger gains in cardiovascular and renal outcomes). Considering the benefits seen for tirzepatide over empagliflozin for intermediate outcomes as well as the current lack of definitive cardiovascular and

renal outcomes for tirzepatide, we judge that tirzepatide is comparable or better (C++) for this comparison.

**Table 3.4. Evidence Ratings**

| <b>Treatment</b> | <b>Comparator</b>      | <b>Evidence Rating</b> |
|------------------|------------------------|------------------------|
| Tirzepatide      | Background Therapy     | B+                     |
| Tirzepatide      | Injectable Semaglutide | C+                     |
| Tirzepatide      | Empagliflozin          | C++                    |

## New England CEPAC Votes

**Table 3.5. New England CEPAC Votes on Comparative Clinical Effectiveness Questions**

| Question  | Yes | No  |
|---|-----|-----|
| Is the currently available evidence adequate to demonstrate that the net health benefit of tirzepatide added to background therapy is superior to that provided by background therapy alone?                              | 13  | 0*  |
| Is the currently available evidence adequate to demonstrate that the net health benefit of tirzepatide added to background therapy is superior to that of adding injectable semaglutide (Ozempic®) to background therapy? | 6   | 7   |
| Is the currently available evidence adequate to demonstrate that the net health benefit of tirzepatide added to background therapy is superior to that of adding empagliflozin (Jardiance®) to background therapy?        | 2   | 10† |

\*This count does not match that shown in the video recording of the voting session because one vote was entered incorrectly into the voting software.

†There was one abstention from this vote.

Note: The patient population for all questions included adults with type 2 diabetes with inadequate glycemic control despite ongoing background antihyperglycemic agent(s).

The panel unanimously voted that the evidence is adequate to demonstrate that tirzepatide plus background therapy is superior to background therapy alone when considering the statistically significant decrease in HbA1c and weight as well as numerical decreases in LDL and SBP observed with tirzepatide versus background therapy alone.

A small majority of the panel voted that the evidence is not adequate to demonstrate that tirzepatide added to background therapy is superior to injectable semaglutide added to background therapy. Panelists who voted with the majority cited the unknowns on potential long-term harms associated with the novel mechanism and that the CVOT are still ongoing (compared to injectable semaglutide which has known CV benefits). Members who voted “Yes” noted that SURPASS-2 was a well conducted trial, and tirzepatide’s HbA1c and weight benefit compared to semaglutide would be meaningful to many patients.

A majority of the panel voted that the evidence is not adequate to demonstrate that tirzepatide added to background therapy is superior to empagliflozin added to background therapy given the lack of head-to-head trials for this comparison and the absence of available CV and renal outcomes for tirzepatide.

## 4. Long-Term Cost Effectiveness

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### 4.1. Methods Overview

We used a patient-level microsimulation relying on the UKPDS-OM2,<sup>10</sup> which was an adaptation of a published microsimulation<sup>52</sup> and an update of the 2019 ICER report on diabetes therapies.<sup>39,53</sup> This particular modeling approach was selected in large part due to the complexity of co-occurring comorbidities in people with T2DM. Our [model analysis plan](#) indicated use of the BRAVO risk engine,<sup>54</sup> however feasibility testing after the publication of the model analysis plan suggested that the information available on BRAVO within the public domain was insufficient to fully implement that engine in a microsimulation model.<sup>54</sup> We therefore used the same risk engine as described in the 2019 ICER report evaluating oral semaglutide, as we deemed this risk engine as the best publicly available source.<sup>39,53</sup>

Consistent with the Comparative Clinical Effectiveness assessment, the intervention of interest was tirzepatide plus background therapy versus (1) injectable semaglutide plus background therapy, (2) empagliflozin plus background therapy, and (3) background therapy alone. For consideration of the equal-value of life years (evLYs) gained measure and the purpose of estimating Health Benefit Price Benchmarks, we identified injectable semaglutide plus background therapy as a primary comparator for this version of the report. We chose injectable semaglutide plus background therapy as the primary comparator because of: (1) mechanism of action overlap between tirzepatide and injectable semaglutide, (2) public and clinical expert feedback that suggested injectable semaglutide is an appropriate comparator that would be considered as an alternative to tirzepatide (rather than added on to tirzepatide), (3) availability of a randomized head-to-head trial on intermediate outcomes, and (4) prior research that suggests injectable semaglutide is cost-effective.<sup>55-57</sup>

The model was informed by clinical trials, the ICER NMA of relevant clinical trials, quality-of-life literature, and validation versus other prior economic models.<sup>53,58,59</sup> The base-case analysis took a health care sector perspective and thus focused on direct medical care costs only. Costs and outcomes were discounted at 3% per year.<sup>60</sup> Because long-term cardiovascular outcomes trial data are immature for the primary intervention under examination in this review, tirzepatide, health benefits for all modeled therapies were informed by intermediate outcomes: HbA1c, body weight, LDL, and SBP, that are predictors in the UKPDS-OM2 risk engine.<sup>10</sup> Because intermediate outcomes alone may not capture a treatment's potential reduction in CVO event risks, as predicted by the UKPDS-OM2 equations, we further multiplied the predicted event risks by the corresponding trial-based CVO hazard ratios and their respective confidence intervals.

The model (Figure 4.1.) is an individual patient-level, Monte Carlo-based microsimulation of costs, quality of life, clinical events, and mortality associated with T2DM among US adults with the

disease. Two modeling steps were used: (1) event microsimulation and (2) calculation of mean results from the pool of simulated patients' lifetime outcomes. Patients, with data from multiple NHANES surveys, were separately simulated through the modeling steps for tirzepatide and each comparator (each added to current ongoing background antihyperglycemic therapy), plus background therapy alone. The two model steps are explained below:

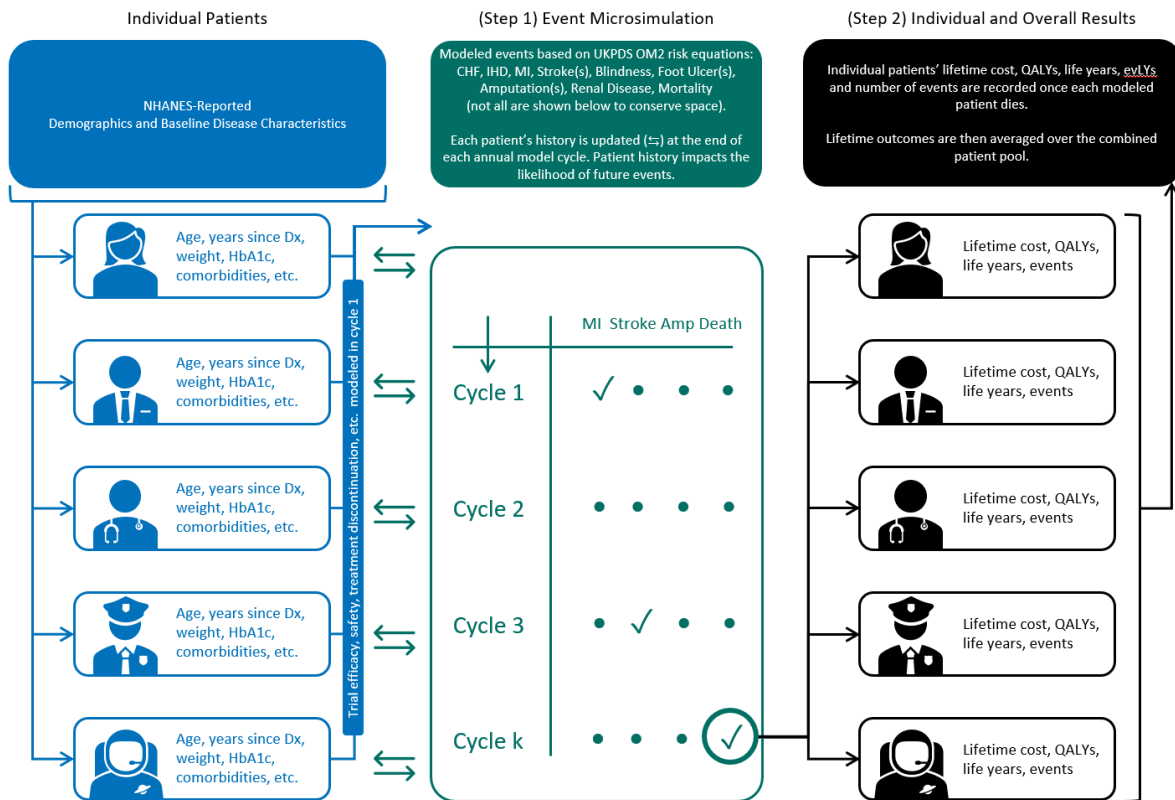
- (1) Event microsimulation.** Each NHANES patient was sequentially run through the event microsimulation. Each model cycle was one year in duration. The UKPDS-OM2 risk equations were used to calculate the incidence of any clinical event(s) and/or mortality in each year until the simulated patient died. Effects of each included therapy, such as change in HbA1c after the first cycle, were included depending on data availability from the NMA. All event and/or mortality associated costs and health state utility weights were applied concurrently. The UKPDS-OM2 risk equations accounted for patient history upon entering the model as well as new clinical events that occurred during the microsimulation; for example, a patient who experienced a first MI in a given year of the microsimulation then had the history of MI covariate turned on in each subsequent year.
- (2) Calculation of mean results.** After each simulated patient died, the model recorded the patient's lifetime cost, quality-adjusted life years (QALYs), equal-value of life years (evLYs), life years, and clinical events. Each outcome was then averaged over the entire pool of patients to derive overall model results.

Further details on the economic modeling methods used are available in [Supplement E](#).

Based on public feedback, the following changes were made to the draft report:

1. Patients whose HbA1c levels exceeded 8.5% added insulin to modeled active therapies rather than replacing active therapies to align with the 2019 T2DM report and reflect common clinical practice.
2. The MACE hazard ratio and uncertainty estimates applied to tirzepatide in the base case were derived from SURPASS-4 results, while the former base case (tirzepatide MACE hazard ratio equal to 1.0) was included as a scenario analysis.
3. 2- and 3-year modeled outcomes compared to existing cardiovascular outcome trials for semaglutide and empagliflozin were added for external validation ([Supplement Table E6](#)).
4. Additional scenario analyses were added to test model assumptions, including those around weight loss utility and risk factor progression.
5. Additional model outcomes were added to the supplement, including disaggregated and undiscounted outcomes, for increased model transparency.
6. Point of clarification: Risk factor progression was reflected in the model first using trial based NMA results and then using published equations for HbA1c and weight change progression for diabetes patients on therapy. The assumption of risk factor progression was then tested in a scenario analysis.

**Figure 4.1. Model Structure**





## 4.2. Key Model Assumptions and Inputs

Below is a list of key model choices:

- Long-term survival and the incidence of diabetes-related clinical events were modeled by applying the UKPDS-OM2 risk equations to a US patient population in an event microsimulation, adjusting the risk equation outputs using available long-term outcome data.<sup>10</sup> The UKPDS-OM2 equations were created from a population of T2DM patients in the United Kingdom and may not reflect US T2DM patient demographics, including differences in race and differences in risk of T2DM-related events.
- Major adverse cardiovascular, heart failure, and nephropathy event rates for injectable semaglutide and empagliflozin were adjusted using data (HRs) from their respective cardiovascular outcomes trials, and cardiovascular event rates for tirzepatide were also adjusted using the HR point estimate and its uncertainty based on the results of SURPASS-4 across pooled tirzepatide doses.<sup>7,8,34</sup> Tirzepatide was not adjusted for heart failure and nephropathy event rates in the base case, reflecting its currently immature CV and renal outcomes and its lack of in-class comparators to use as proxies.
- Quality of life was modeled within QALYs using projected patient survival weighted using regression-based disutilities for each diabetes-related complication experienced in each model cycle.
- The model included all treatment costs associated with each individual drug regimen, including drug acquisition costs, downstream treatments such as insulin, and supportive care costs (e.g., clinician visits and self-monitoring), as well as costs associated with diabetes-related complications experienced in each model cycle.
- All model outcomes were calculated over a lifetime time horizon.<sup>60</sup>
- Life-years, QALYs, and health care cost outcomes were discounted at 3% per year.<sup>60</sup>

Our model included several assumptions stated below.

**Table 4.1. Key Model Assumptions**

| <b>Assumption</b>   | <b>Rationale</b>   |
|---|--|
| Patient diabetes outcomes were simulated using the UKPDS-OM2 equations; predicted model outcomes for MACE, HF, and nephropathy were adjusted by hazard ratios to align with existing trial evidence where possible.   | Accurately modeling the complexity of diabetes disease progression is notoriously difficult. The UKPDS equations remained the best available tool for this modeling exercise despite the known limitations when applied to a modern US population. These limitations were addressed in multiple ways, including hazard ratio adjustments using available clinical evidence and short-term external validation. |
| Initial patient clinical characteristics were based on NHANES survey data.  | NHANES is a nationally representative and federally funded survey repeated every two years in the United States, uniquely capturing the wide range of demographic and clinical data necessary to understand and predict diabetes disease progression in a modern population.   |
| Modeled risk equation adjustment for CV and renal outcomes for active comparators with CVOT data is maintained while patients remain on treatment.  | Active treatment comparators (injectable semaglutide and empagliflozin) have data from CVOTs. We adjusted the event prediction output of the risk equations based on how the model outcomes compare to those trial outcomes in the base-case analysis.   |
| Modeled risk equation adjustment for CV and renal outcomes for tirzepatide is maintained while patients remain on treatment.  | Long-term effectiveness of tirzepatide is currently unknown. We evaluated the impact of not applying any adjustment of relative effect to tirzepatide for changes in heart failure and renal outcomes in the base case. Tirzepatide's MACE outcomes were adjusted based on SURPASS-4 findings in the base case.  |
| Ongoing background therapy was assumed the same for all comparators, and all patients in all model arms who discontinue treatment (including those on background therapy alone) transition to insulin.  | The goal is to evaluate direct comparisons among the treatments of interest and not multiple possible treatment sequences.   |
| Patients discontinued their add-on treatment at a rate of 9.1% in the second model cycle. The discontinuation rate was derived from the EMPA-REG EXTEND trial, the only trial to present discontinuation data contingent on a successful initial treatment period. Those who were on add-on treatment after the second model cycle were assumed to remain on add-on treatment and received the corresponding treatment benefits, risks, and costs for their remaining life. Patients whose HbA1c reached 8.5% or above during any model cycle after the first were assumed to initiate insulin as add-on treatment. | <p>Equivalent discontinuation was assumed for active treatments after the initial model cycle as this measure was not included in the NMA and we had insufficient evidence to suggest differential long-term discontinuation across all therapies.</p> <p>We evaluated changes to the 8.5% HbA1c threshold for adding insulin therapy in scenario analyses.</p>  |

The patient population for this analysis was derived from the National Health and Nutrition Examination Survey (NHANES), conducted by the United States Centers for Disease Control and Prevention. Survey participants from years 2013-2014, 2015-2016, and 2017-2018 were included if they had self-reported diabetes, HbA1c levels greater than 7%, and were already taking metformin (with or without sulfonylureas), but not another type of add-on diabetes therapy. This resulted in 387 unique patients, whose characteristics are described in Table 4.2, and whose patient-level baseline clinical inputs were used to power the microsimulation model.

**Table 4.2. Base-Case Model Cohort Characteristics**

| Description                           | Mean (SD) or Percentage (N) |
|---------------------------------------|-----------------------------|
| <b><u>Patient Characteristics</u></b> |                             |
| Age at Time of survey                 | 60.4 (11.53)                |
| % Female                              | 42.9% (166)                 |
| Duration of disease                   | 9.9 (7.91)                  |
| Race                                  | 26.6% (103)                 |
| White, %                              | 22.7% (88)                  |
| Black or African American, %          | 14.5% (56)                  |
| Asian, %                              | 11.4% (44)                  |
| Hispanic, %                           | 24.8% (96)                  |
| Other                                 | 21.2% (82)                  |
| Weight (kg)                           | 88.8 (24.94)                |
| BMI (kg/m <sup>2</sup> )              | 31.9 (7.55)                 |
| HbA1c (%)                             | 8.4 (1.54)                  |
| LDL (mmol/L)                          | 2.7 (0.93)                  |
| SBP (mmHg)                            | 132.5 (18.88)               |
| % Current smokers                     | 36.7% (142)                 |
| % on Metformin                        | 100.0% (387)                |
| % on Sulfonylurea                     | 42.9% (166)                 |
| <b><u>Disease History</u></b>         |                             |
| Myocardial infarction                 | 5.9% (23)                   |
| Stroke                                | 4.4% (17)                   |
| Heart failure                         | 4.1% (16)                   |
| Ischemic heart disease                | 7.8% (30)                   |
| Angina                                | 4.1% (16)                   |
| Renal disease                         | 15.8% (61)                  |

HbA1c: hemoglobin A1c, LDL: low-density lipids, N: number of subjects in full analysis set, SBP: systolic blood pressure, SD: standard deviation

The efficacy of tirzepatide, injectable semaglutide, and empagliflozin as compared to background therapy alone were measured via intermediate outcomes such as changes in HbA1c, lipid levels, blood pressure, and body weight. Intermediate outcome efficacy estimates for each active comparator against background therapy were derived from the NMA described in [Section 3](#) and were applied after the first cycle of the model. Each model cycle subsequently utilized updated patient-level input parameters based on the predictions of the UKPDS-OM2 risk equations and

patient history. UKPDS equations, which are available in the public domain, estimate the probability of 12 diabetes complication events and four mortality events in each cycle.<sup>10</sup> To supplement UKPDS-OM2 output, time-varying risk factor values of HbA1c and weight were calculated using additional published equations.<sup>61</sup> To adjust the UKPDS event predictions to existing trial data, we multiplied the probability of events occurring predicted by UKPDS equations by the relevant HR in each model cycle for three event measurements: composite MACE, heart failure, and renal events. Thus, the probabilities informed by the regression equations were adjusted by the HRs. These HRs were abstracted directly from the semaglutide and empagliflozin CVOTs, and from the SURPASS-4 trial in the case of tirzepatide.

Health state utilities and mortality risk equations are further detailed in [Supplement E2](#).

Calculated net drug prices were applied to each patient while they remained on treatment. For each comparator, we obtained net pricing estimates from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price.<sup>62</sup> We estimated net prices by comparing the most recent four-quarter averages (i.e., third quarter of 2020 through second quarter of 2021) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (accessed September 2021) to arrive at an estimated net price per unit. Tirzepatide was given a placeholder price equal to semaglutide, the only suitable proxy drug in the injectable GLP-RA drug class, until its price is publicly available. Drug cost inputs can be found in Table 4.3.

**Table 4.3. Drug Cost Inputs**

| Drug  | WAC per 30-Pill Bottle/Pen   | Net Price Per 30-Pill Bottle/Pen | Discount From WAC | Net Price per Year‡       |
|---|------------------------------|----------------------------------|-------------------|---------------------------|
| <b>Tirzepatide*</b>                                 | (4 weekly doses)             | (4 weekly doses)                 | -                 | Placeholder<br>\$4,643.50 |
| <b>Semaglutide (Ozempic®) 4 mg/3 mL pen†</b>        | \$851.60<br>(4 weekly doses) | \$355.97<br>(4 weekly doses)     | 58.20%            | \$4,643.50                |
| <b>Empagliflozin (Jardiance®) 30-tablet bottle§</b> | \$548.54                     | \$107.51                         | 80.40%            | \$1,402.43                |
| <b>Metformin#</b>                                   | \$0.83                       | -                                | -                 | \$10.04                   |
| <b>Sulfonylureas‡</b>                               | \$5.05                       | -                                | -                 | \$61.48                   |

WAC: wholesale acquisition cost

\*As a placeholder, we used the net price of Ozempic® (semaglutide), which is a once weekly injectable GLP-1; WAC pricing and discounts reflect the number of pen doses and quantity of pens necessary for Ozempic® use.

†The 4 mg/3 mL Ozempic® pen includes four 1 mg doses; assumes 1 mg weekly dose.

‡One year = 365.25 days or 52 weeks

§Assumes 25 mg daily dose of empagliflozin. Source: Red Book.

#Assumes 1000 mg daily dose of metformin. Source: Red Book.

‡Assumes 20 mg daily dose of glipizide. Source: Red Book.

The average clinical costs of experiencing a diabetes-related event within a cycle, as well as the average annual clinical costs of subsequent years after a health event, were adapted from the literature.<sup>52,63,64</sup> Patients were able to experience events concurrently within the model. Costs were inflated to 2021 USD. Additional details on the economic model can be found in [Supplement E](#).

## 4.3. Results

### Base-Case Results

Due to the characteristics of the microsimulation, the model's base-case results are presented as the mean and 95% credible range estimates from probabilistic sensitivity analyses, by jointly varying all model parameters and UKPDS-OM2 risk engine equation coefficients over 3,000 simulations per patient, then calculating 95% credible range estimates for each model outcome based on the distributions of those simulations. The base-case discounted results are presented in Table 4.4., with incremental comparisons of tirzepatide to the three comparators presented in Table 4.5. Equal value of life years gained were not reported given tirzepatide average life years were not greater than injectable semaglutide average life years. Disaggregated base-case results, including costs and disease-related events, are available in the [Supplement Table E3.1](#) and undiscounted results are available in [Supplement Table E3.2](#).

**Table 4.4. Results for the Base Case for Tirzepatide and Comparators: Injectable Semaglutide, Empagliflozin, and Background Therapy – Mean (95% Credible Range)\***

| Treatment                     | Add-On Drug Cost |                       | Total Cost (including background therapy and insulin) |                         | QALYs |                    | Life-years‡ |                    |
|-------------------------------|------------------|-----------------------|---|-------------------------|-------|--------------------|-------------|--------------------|
|                               | Mean             | 95% Credible Range    | Mean  | 95% Credible Range      | Mean  | 95% Credible Range | Mean        | 95% Credible Range |
| <b>Tirzepatide†</b>           | \$40,500         | (\$38,200 - \$42,900) | \$306,000   | (\$275,000 - \$339,000) | 4.90  | (4.68 – 5.12)      | 9.36        | (8.91 – 9.83)      |
| <b>Injectable Semaglutide</b> | \$41,200         | (\$38,800 - \$43,500) | \$309,000   | (\$280,000 - \$339,000) | 4.85  | (4.64 – 5.05)      | 9.53        | (9.08 – 9.97)      |
| <b>Empagliflozin</b>          | \$12,000         | (\$11,300 - \$12,700) | \$276,000   | (\$248,000 - \$305,000) | 4.60  | (4.40 – 4.79)      | 9.17        | (8.73 – 9.61)      |
| <b>Background Therapy</b>     | \$0              | NA                    | \$262,000   | (\$235,000 - \$291,000) | 4.13  | (3.95 – 4.33)      | 8.34        | (7.93 – 8.77)      |

QALY: quality-adjusted life-year

\*All costs and outcomes discounted at 3% annually

†Using a Placeholder Price equal to the net price of semaglutide

‡Equal value of life years gained were not reported given tirzepatide average life years were not greater than injectable semaglutide average life years.

Of the known drug costs, injectable semaglutide had the highest lifetime drug costs at \$41,200 (a placeholder cost was used for tirzepatide). For total lifetime costs, including background treatment costs and costs of cardiovascular and renal complications, injectable semaglutide had the highest costs at approximately \$309,000, followed by tirzepatide (\$306,000), empagliflozin (\$276,000), and background therapy (\$262,000). Tirzepatide was estimated to produce the highest QALYs of all considered therapies, however the QALY 95% credible ranges for active comparators overlapped. All active comparators produced higher QALYs than background therapy alone without overlapping credible ranges.

**Table 4.5. Incremental Cost-Effectiveness Ratios for the Base Case – Mean (95% Credible Range)<sup>§</sup>**

| Treatment    | Comparator               | Cost per QALY Gained         |                               | Cost per Life Year Gained‡ |                             |
|--------------|--------------------------|------------------------------|-------------------------------|----------------------------|-----------------------------|
|              |                          | Mean                         | 95% Credible Range            | Mean                       | 95% Credible Range          |
| Tirzepatide* | Injectable Semaglutide   | Less Costly, More Effective† | (-\$1,500,000 to \$1,400,000) | \$17,000                   | (-\$709,000 to \$634,000)   |
| Tirzepatide* | Empagliflozin            | \$101,000                    | (-\$55,000 to \$331,000)      | \$160,000                  | (-\$951,000 to \$1,300,000) |
| Tirzepatide* | Background Therapy Alone | \$58,000                     | (\$11,000 to \$99,000)        | \$44,000                   | (\$10,000 to \$83,000)      |

QALY: quality-adjusted life-year

\*Using a Placeholder Price equal to the net price of semaglutide

†Although the mean ICER point value indicates lower cost and greater health benefit of tirzepatide over semaglutide, neither of the ratio's inputs (savings of \$2,900 for an additional 0.05 QALYs) were statistically different from zero

‡Equal value of life years gained were not reported given tirzepatide average life years were not greater than injectable semaglutide average life years.

§Ratios and credible ranges displayed in table are the mean values across all microsimulations rather than derivations of output in Table 4.4.

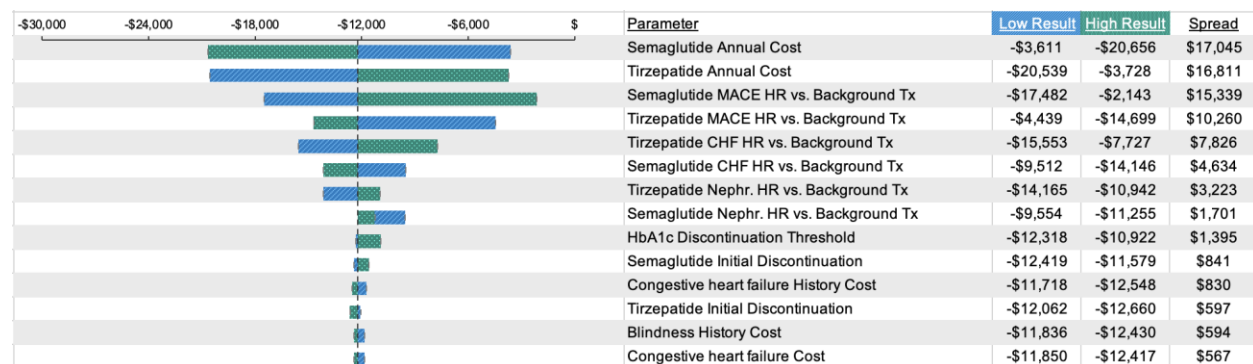
The incremental cost-effectiveness measures reported in Table 4.5. are based on a placeholder price equal to the net value of injectable semaglutide and should be interpreted with caution. Further, 95% credible ranges for incremental cost-effectiveness ratios should be interpreted with caution due to: the ratio form of this measure, negative findings can carry different meanings, and placeholder pricing may not reflect paid amounts. Therefore, uncertainty presented in the probabilistic sensitivity analyses is likely more helpful in understanding its impact on the findings.

## Sensitivity Analyses

One-way sensitivity analyses (OWSA) to identify the impact of parameter uncertainty and key drivers of model outcomes were performed. Details about the sensitivity analysis methods can be found in [Supplement E4](#). Compared to injectable semaglutide, the inputs that were associated with the largest variation in incremental costs were annual costs of semaglutide and tirzepatide, semaglutide and tirzepatide event hazard ratios, and the HbA1c discontinuation threshold (Figure 4.2.). The reader should only use these one-way sensitivity analysis findings to gain insights into the

general magnitude of impact that unique model inputs have on incremental costs (and health gains). The base-case incremental results remain a more robust average estimate compared with the central values displayed in the one-way sensitivity figures given the added computer simulation requirements needed for the sensitivity analyses. The tornado diagram for incremental costs was truncated to include inputs with at least a \$500 difference between the high and low value. Compared to injectable semaglutide, the inputs that were associated with the largest variation in incremental QALYs were the tirzepatide and semaglutide event hazard ratios, the HbA1c discontinuation threshold, and semaglutide and tirzepatide effect on body weight (Figure 4.3.). The tornado diagram for incremental QALYs was truncated to include inputs with more than a 0.01 QALY difference between the high and low value. Additional tornado diagrams are presented in [Supplement E4](#).

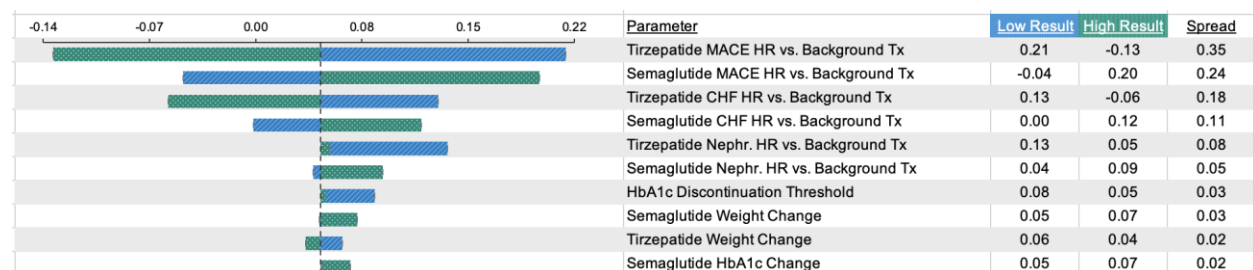
**Figure 4.2. Incremental Costs Tornado Diagram (Tirzepatide vs. Injectable Semaglutide)\***



CHF: congestive heart failure, HbA1c: Hemoglobin A1c/glycosylated hemoglobin, HR: hazard ratio, MACE: major adverse cardiovascular event, Tx: treatment

\*Using a placeholder price for tirzepatide

**Figure 4.3. Incremental QALYs Tornado Diagram (Tirzepatide vs. Injectable Semaglutide)**



CHF: congestive heart failure, HbA1c: Hemoglobin A1c/glycosylated hemoglobin, HR: hazard ratio, MACE: major adverse cardiovascular event, QALY: quality-adjusted life-year, Tx: treatment

Unlike a typical cohort model, our probabilistic sensitivity analysis for this microsimulation is presented as the base-case results in order to account for patient and risk equation uncertainty. The cost-effectiveness acceptability curves from the base case are presented in [Supplement Figure E5](#).

## Scenario Analyses

Multiple scenario analyses can be found in [Supplement E5](#). We sought to produce model estimates using a modified societal perspective and found a paucity of data to inform such calculations for a simulation. However, we present a calculated estimate of cost-effectiveness under a modified societal perspective using an estimate of productivity costs saved based on assumptions that fill in missing data. The results of these calculations are also presented in the Supplement.

## Threshold Analyses

The annual drug costs at which tirzepatide plus background therapy would reach cost-effectiveness thresholds ranging from \$50,000 to \$200,000 per QALY gained compared to semaglutide plus background therapy, empagliflozin plus background therapy, and background therapy alone, are presented below in Table 4.6. Equal value of life years gained were not reported given tirzepatide average life years were not greater than injectable semaglutide average life years.

**Table 4.6. Cost per Outcome Threshold Analysis Results for Tirzepatide vs. Background Therapy**

|  | Net Price per Unit | Annual Price to Achieve \$50,000 per outcome | Annual Price to Achieve \$100,000 per outcome | Annual Price to Achieve \$150,000 per outcome | Annual Price to Achieve \$200,000 per outcome |
|--|--------------------|--|---|---|---|
| <b>Tirzepatide plus Background Therapy vs. Semaglutide plus Background Therapy</b>   |                    |  |   |   |   |
| <b>Mean QALYs Gained</b>   | To be determined   | \$5,200                                      | \$5,500                                       | \$5,700                                       | \$6,000                                       |
| <b>Tirzepatide plus Background Therapy vs. Empagliflozin plus Background Therapy</b> |                    |  |   |   |   |
| <b>Mean QALYs Gained</b>   | To be determined   | \$3,000                                      | \$4,600                                       | \$6,200                                       | \$7,700                                       |
| <b>Tirzepatide plus Background Therapy vs. Background Therapy Alone</b>              |                    |  |   |   |   |
| <b>Mean QALYs Gained</b>   | To be determined   | \$4,000                                      | \$8,000                                       | \$12,000                                      | \$15,900                                      |

QALY: quality-adjusted life-year

Net price for tirzepatide has not been publicly stated at the time of this report; Equal value of life years gained were not reported given tirzepatide average life years were not greater than injectable semaglutide average life years.



## Model Validation

We used several approaches to validate the microsimulation model's output. First, we provided the preliminary methods to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined the model approach (outlined in Section 4.1). Second, we varied the model input parameters to evaluate the face validity of changes to those inputs on the results in the OWSA. We also performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also shared the model with the manufacturers for external verification following the publication of the draft report.

For further model validation and calibration, we compared the cardiovascular and renal trial outcomes versus model projections in the revised report, found in [Supplement Section E6](#). This comparison was informed by microsimulations on modified patient populations and for a shorter time horizon to reflect specific trial conditions more accurately.

## Uncertainty and Controversies

This model represents a simplified version of a complex disease and should therefore be interpreted with its limitations in mind. Cost and long-term outcome data for tirzepatide were unavailable at the time of the report and could not be used to validate its clinical results; any economic output for tirzepatide is based on a placeholder price and the results should not be interpreted as factual. Additionally, there are noted limitations to the UKPDS-OM2 risk equations used for this analysis, including that they were developed based on a patient cohort from the United Kingdom in decades past, had a notably different demographic and clinical patient population than generally seen in the current United States, and may not fully capture the impact of weight loss on CV and renal outcomes. Our choice to use UKPDS-OM2 risk equations was made based on lack of feasible alternatives at the time, and adjustments were used in an attempt to ensure the model estimates aligns with clinical evidence. We present shorter time horizon simulations, aligned with the cardiovascular and renal outcomes trials for semaglutide and empagliflozin, in the supplement in order to compare our model event outcomes with those found in the trials to understand the chosen model's impact on our estimates.

Finally, we acknowledge challenges in modeling tirzepatide given the immaturity of the evidence of its impact on micro- and macrovascular outcomes. In the threshold analyses, we compared tirzepatide to injectable semaglutide and estimated the health gains of tirzepatide through changes in intermediate outcomes, assuming the same hazard ratio point estimate as injectable semaglutide for composite MACE and no adjustment to other outcomes to reflect tirzepatide's cardiovascular safety study. The scenario analysis that includes tirzepatide's changes only through intermediate outcomes, with no adjustment from hazard ratios, provides estimates of the potential relative impact on health outcomes if the trends observed in tirzepatide's cardiovascular safety study are not sustained long-term.

## 4.4 Summary and Comment

We used a patient-level microsimulation of T2DM patients taking an add-on therapy over a lifetime time horizon to assess the cost-effectiveness of the novel injectable agent tirzepatide in addition to background therapy against injectable semaglutide plus background therapy, empagliflozin plus background therapy, and background therapy alone. Tirzepatide had the highest average lifetime discounted QALYs of all considered therapies, however the QALY 95% credible ranges for active comparators overlapped. Using a placeholder price equal to injectable semaglutide, the incremental costs per QALY gained for tirzepatide were around or under \$100,000 versus all comparators with mean differences in health gains and costs being smallest in comparison to injectable semaglutide. Uncertainty analyses suggested a wide range of plausible cost-effectiveness estimates for tirzepatide. These results paired with tirzepatide's unknown price preclude strong conclusions about its cost-effectiveness at this time.

## 5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

**Table 5.1. Contextual Considerations**

| Contextual Consideration   | Relevant Information   |
|--|--|
| Acuity of need for treatment of individual patients based on the severity of the condition being treated | Although there are multiple medication options for the treatment of T2DM, nearly half of patients have not reached adequate glycemic control. <sup>1</sup> Thus, additional options for treatment are beneficial.  |
| Magnitude of the lifetime impact on individual patients of the condition being treated                   | Patients with inadequately controlled T2DM are at risk for microvascular and macrovascular complications, which can substantially affect both quality of life and longevity. Additionally, many patients with T2DM are overweight or obese, and weight loss may be of benefit to prevent complications of obesity. |
| Other (as relevant)  | NA   |

**Table 5.2. Potential Other Benefits or Disadvantages**

| Potential Other Benefit or Disadvantage   | Relevant Information   |
|---|--|
| Patients' ability to achieve major life goals related to education, work, or family life                          | Prevention or delay of microvascular and macrovascular complications may allow for greater work or educational productivity.   |
| Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life | Prevention or delay of microvascular and macrovascular complications may lessen caregiving burden over the lifetime.   |
| Patients' ability to manage and sustain treatment given the complexity of regimen                                 | Preliminary evidence suggests tirzepatide's medication delivery device may be preferred by some patients compared with the delivery device of other GLP-1 RAs. In two studies measuring preference for injection devices, more T2D patients preferred descriptions of tirzepatide/dulaglutide injection processes and preferred performing mock tirzepatide/dulaglutide injections over mock semaglutide injections. <sup>65 66</sup>  |
| Health inequities   | T2DM disproportionately affects minority populations, and significant disparities exist in prevalence, disease control, and rates of complications. <sup>67</sup> ICER calculated the Health Improvement Distribution Index, looking at the relative proportion of any health gains from treatment of T2DM for the following groups with a higher prevalence of T2DM than the general US population ( <a href="#">see Supplement A1</a> )*:<br>American Indian/Alaska Native = 1.4<br>Hispanic = 1.2<br>Asian Indian = 1.2<br>Non-Hispanic Black = 1.1 |
| Other (as relevant)   | NA   |

\*ICER acknowledges the sensitivities around the naming conventions of these racial and ethnic categories, and for the purposes of the Health Improvement Distribution Index, we attributed these based on the populations analyzed in the 2020 National Diabetes Statistics Report published by the Centers for Disease Control and Prevention.<sup>1</sup>

The main potential other benefit of tirzepatide relates to its impact on obesity and obesity-related diseases and complications. The majority of patients in the US with T2DM are overweight or obese, and at risk for obesity-related complications – e.g., obstructive sleep apnea, nonalcoholic fatty liver disease, high blood pressure, cardiovascular disease, and osteoarthritis – any medication that induces weight loss could have beneficial effects outside of its impact on glycemic control. Tirzepatide appears to induce more substantial weight loss in patients than its comparator drugs, and thus may have an impact on obesity-related diseases as well.

Additionally, a substantial number of patients achieved near-normal glycemic control (defined as a HbA1c <5.7%) in SURPASS-2. Not only is this a boost to patients, who cite glycemic control as one of the more important outcomes for managing their diabetes, but it may also slow progression of disease, particularly if achieved early in the disease course.<sup>18</sup> Prevention of progression and potentially of development of the micro- and macrovascular complications of T2DM could both

improve the productivity of patients and lessen caregiving burden. For example, prevention of diabetic neuropathy may lead to fewer amputations and thus less disability.

## New England CEPAC Votes

At the public meeting, the New England CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the [ICER Value Assessment Framework](#).

**When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for type 2 diabetes on the basis of the following contextual considerations:**

| Contextual Consideration   | Very Low Priority | Low priority | Average priority | High priority | Very high priority |
|--|-------------------|--------------|------------------|---------------|--------------------|
| Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability | 2                 | 2            | 7                | 1             | 1                  |
| Magnitude of the lifetime impact on individual patients of the condition being treated                                       | 0                 | 0            | 3                | 6             | 4                  |

A majority of the panel voted that based on the acuity of need for treatment of individual patients with type 2 diabetes, average priority should be given to any effective treatment. However, the panelists largely agreed on the high priority regarding the magnitude of lifetime impact on patients with type 2 diabetes, acknowledging the patient expert testimony on how unmanaged diabetes can lead to other complications. We also heard how having more treatment options available to patients to reduce the risk of developing these complications over the long-term is extremely important, particularly for patients diagnosed at a younger age.

**What are the relative effects of tirzepatide added to background therapy versus injectable semaglutide (Ozempic®) added to background therapy on the following outcomes that inform judgment of the overall long-term value for money of tirzepatide?**

| Potential Other Benefit or Disadvantage   | Major Negative Effect | Minor Negative Effect | No Difference | Minor Positive Effect | Major Positive Effect |
|---|-----------------------|-----------------------|---------------|-----------------------|-----------------------|
| Patients' ability to achieve major life goals related to education, work, or family life                          | 0                     | 0                     | 7             | 6                     | 0                     |
| Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life | 0                     | 0                     | 9             | 4                     | 0                     |
| Society's goal of reducing health inequities  | 0                     | 0                     | 13            | 0                     | 0                     |

About half of the panel voted that tirzepatide would have a minor positive effect on patients' ability to achieve life goals related to education, work, or family life, but a bare majority voted that tirzepatide would make no difference compared to injectable semaglutide. This vote was driven largely by patient and clinical expert testimony around potential self-injection device preferences between tirzepatide and injectable semaglutide (if approved, tirzepatide is expected to use an autoinjector). We also heard that there is little additional risk of hypoglycemia for tirzepatide versus injectable semaglutide based on the SURPASS-2 trial which we heard is important to patients in maintaining their independence in daily life.

A majority of the panel voted that tirzepatide would make no difference on caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life, though some members of the panel raised that some patients may need a caregiver to administer injections.

The panel unanimously voted that tirzepatide would make no difference on society's goal of reducing health inequities compared to injectable semaglutide. The panel heard clinical expert testimony that unless there are insurance benefits, they don't see any potential effect on inequities unless this drug is or is not offered equally to all patients.

## 6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with the tirzepatide are presented in Table 6.1. below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between \$100,000 and \$150,000 per QALY or per evLY gained. Based on our model simulations, we arrive at a HBPB for tirzepatide from \$5,500 to \$5,700 per QALY gained compared to injectable semaglutide plus background therapy. Equal value of life years gained were not reported given tirzepatide average life years were not greater than injectable semaglutide average life years. Discounting from WAC to reach the threshold price for tirzepatide is not applicable as it is currently based on a placeholder WAC price and should be updated when WAC pricing is established.

**Table 6.1. Annual Cost-Effectiveness Health Benefit Price Benchmarks for Tirzepatide plus Background Therapy vs. Semaglutide plus Background Therapy**

| Outcome for Annual HBPB Calculation   | Annual WAC | Annual Price at \$100,000 Threshold | Annual Price at \$150,000 Threshold | Discount from WAC to Reach Threshold Prices |
|---|------------|-------------------------------------|-------------------------------------|---|
| Tirzepatide plus Background Therapy vs. Semaglutide plus Background Therapy |            |                                     |                                     |   |
| QALYs Gained  | NA*        | \$5,500                             | \$5,700                             | NA*   |

HBPB: health benefit price benchmark, QALY: quality-adjusted life-year, WAC: wholesale acquisition cost

\*Not applicable (NA) as placeholder prices were used

### New England CEPAC Votes

Long-term value for money votes were not taken at the public meeting because a net price for tirzepatide was not available.

## 7. Potential Budget Impact

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### 7.1. Overview of Key Assumptions

Using results from the cost-effectiveness model, we estimated the potential budget impact of adding tirzepatide to current background therapy for patients with T2DM with inadequate glycemic control. We used the tirzepatide placeholder price from the base-case analysis (placeholder price of \$4,643.50 per year) and three threshold prices (at \$50,000, \$100,000, and \$150,000 per QALY) when comparing tirzepatide plus background therapy to injectable semaglutide plus background therapy in order to align with the HBPB comparisons made within the cost-effectiveness analyses. Potential budget impact is defined as the total differential cost of using tirzepatide rather than the relevant existing therapy for the treated population, calculated as intervention costs minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon.

The analysis included the estimated number of individuals in the US who would be eligible for treatment with tirzepatide. To estimate the size of the potential candidate population for treatment, we used inputs for the total US adult population size (~265 million)<sup>68</sup>, overall T2DM prevalence (14.6%)<sup>69</sup>, proportion of patients with diagnosed T2DM (76.7%)<sup>69</sup>, and the proportion of patients having failed background therapy and considering a second-line treatment and thus eligible for tirzepatide (16.2%).<sup>70</sup> Applying these sources results in estimates of 4,800,000 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate tirzepatide treatment in each of the five years, or approximately 960,000 patients per year. Tirzepatide drew market share proportionally from each of the model comparators over the five-year time horizon.

Market shares were derived from analyst projections based on primary market research, company reports, and key opinion leader surveys.<sup>71</sup> We set the initial market shares for injectable semaglutide equal to a calculated 2021 market share for the GLP-1 RA class (15.1%), while the market share for empagliflozin was set to a calculated 2021 market share for the SGLT-2 inhibitor class (12.7%). The remaining market share was attributed to background therapy.

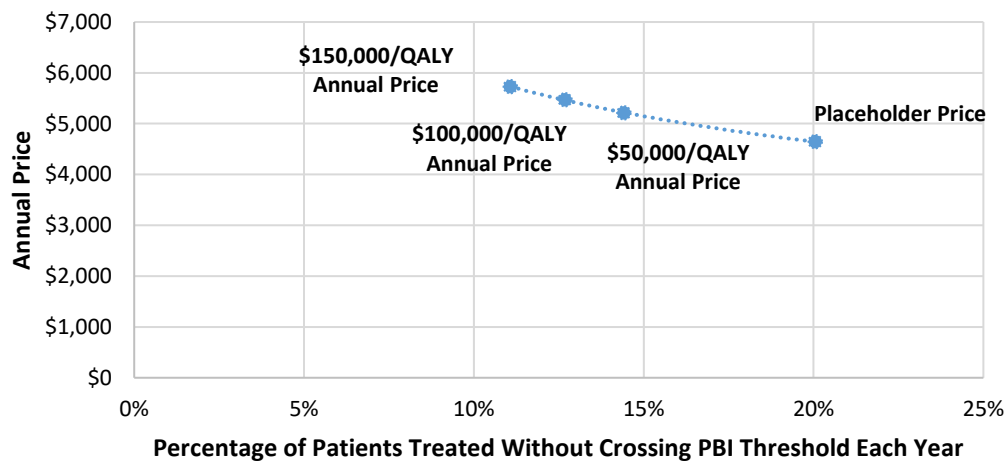
The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at select prices within five years without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2021-2022, the five-year annualized potential budget impact [threshold](#) that should trigger policy actions to manage access and affordability is calculated to be approximately \$734 million per year for new drugs.



## 7.2. Results

Assuming the tirzepatide placeholder price of \$4,643.50 per year, 20.1% of the eligible patients could be treated within five years (assuming 20% uptake each year) without crossing the ICER potential budget impact threshold of \$734 million per year. In contrast, 14.4%, 12.7%, and 11.1% of eligible patients could be treated within five years without crossing the ICER potential budget impact threshold at the annual price to reach \$50,000 per QALY (\$5,200), \$100,000 per QALY (\$5,500), or \$150,000 per QALY (\$5,700) versus injectable semaglutide plus background therapy, respectively. Figure 7.1. depicts the potential budgetary impact of tirzepatide at the placeholder price and the three threshold prices. Due to a large eligible population, the budget impact results were very sensitive to the price of tirzepatide and corresponding cost offsets. For instance, a \$129 increase in tirzepatide annual placeholder price (~3%) led to a 10% relative reduction in the number of T2D patients that could be treated without crossing the ICER potential budget impact threshold.

**Figure 7.1. Budgetary Impact of Tirzepatide in Adults with T2DM at Placeholder Price and Threshold Annual Prices**



### Access and Affordability Alert

As no publicly available or otherwise known price exists for tirzepatide, an Affordability and Access Alert was not issued during the public meeting; however, affordability of and access to tirzepatide for patients with T2DM is of utmost importance given the large eligible patient population and significant unmet needs in the T2DM space.

## 8. Policy Recommendations

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Following its deliberation on the evidence, the New England CEPAC engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of tirzepatide for type 2 diabetes. The policy roundtable members included 2 patient advocates, 2 clinical experts, 1 payer, and 2 representatives from a pharmaceutical company. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

### All Stakeholders

#### *Recommendation 1*

***All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with type 2 diabetes mellitus (T2DM) are introduced in a way that will help reduce health inequities.***

Despite the multitude of treatments available for T2DM, almost half of patients have not met their glycemic target. There are racial and ethnic disparities in both prevalence and treatment in the US, with minorities both more likely to have T2DM and have higher average HbA1c than non-Hispanic whites.<sup>1,72</sup> Therefore, additional treatment options, particularly those that are effective in lowering glucose, promoting weight loss, and decreasing cardiovascular and renal complications, have the potential to have a greater impact in minority communities. However, efforts are needed to ensure that new therapies for T2DM, such as tirzepatide, improve the health of patients and families and do not aggravate existing health inequities.

Clinical experts and patients highlighted that the high cost of new therapies may worsen disparities in accessing care. This may be due to lack of health insurance that limits access to physicians and the new therapies that they prescribe, or high deductible payments even for those with insurance may result in steep out of pocket costs. Cost of care is not the only factor that may contribute to health inequities. Lack of culturally appropriate information to educate patients with T2DM and their families about lifestyle changes and treatments, as well as inequities in offering new technologies and treatments to minority populations may also play significant roles in existing health disparities relative to T2DM treatment.

To address these concerns:

Manufacturers should take the following actions:

- Do not assume that coupon programs for some eligible patients are sufficient to address affordability more broadly; instead, ensure that the set price for new treatments for T2DM is in fair alignment with added benefits for patients.
- Partner with patient groups, clinicians, and researchers to develop strategies to recruit a more diverse patient population in clinical trials reflective of the broader T2DM population.

Payers should take the following actions:

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access for vulnerable patients.
- Consider developing quality measures to incentivize clinicians to ensure fair distribution of treatments (e.g., a measure reporting the percentage of patients with ASCVD or CKD who are on a GLP-1 RA or SGLT-2 inhibitor).

Health systems should take the following actions:

- Consider developing programs tailored to their health system needs to identify patients who are eligible for, and who would benefit from, newer therapies with cardiovascular or renal benefit such as GLP-1 RAs or SGLT-2 inhibitors.
- Support primary care physicians and endocrinologists, who care for the majority of patients with T2DM, in developing programs to ensure equal prescribing of appropriate therapies. For example, supporting e-consults to specialists, developing order sets, and delivering culturally appropriate care. Examples of resources that may assist health systems in implementing programs include: the e-consult Workgroup (<https://econsultworkgroup.com/>); e-consults in the safety-net setting from San Francisco General Hospital (<https://www.careinnovations.org/resources/facilitating-care-integrationintegrating-primary-care-and-specialty-careinnovator-highlight-san-francisco-general-hospitals-ereferral-system/>); and protocols and order sets compiled by the American Association of Clinical Endocrinologists (<https://pro.aace.com/disease-state-resources/diabetes/depth-information/protocols-and-order-sets>).

Clinicians should take the following actions:

- Clinicians caring for T2DM patients should consider organizing team-based care that prioritizes decreasing health inequities in the delivery of diabetes care, including ensuring that guideline-based treatment is offered to all patients and delivering culturally appropriate diabetes education. Examples of programs to emulate include the Latinx and Asian American Diabetes Initiatives at Joslin Diabetes Center (<https://www.joslin.org/patient-care/multicultural-programs>); the Centers for Disease Control Native Diabetes Wellness Program (<https://www.cdc.gov/diabetes/ndwp/index.html>); and Diabetes Education Online from the UCSF Diabetes Teaching Center (<https://dte.ucsf.edu/>, website and materials available in English, Spanish, and Chinese).

Patient groups should take the following actions:

- Ensure that their leadership is representative of and informed with input from diverse T2DM patients.
- Partner with other stakeholders to develop and disseminate educational materials and programs about prevention and management of T2DM that are culturally sensitive and language-concordant with the target population(s).
- Continue to advocate for greater diversity in clinical trial populations, reflective of the T2DM population in the US, and work with manufacturers and researchers to develop effective strategies for the recruitment and retention of minority participants in clinical trials of T2DM therapies.

## **Recommendation 2**

***Federal and state policymakers, payers, and health systems should work together to ensure that prior authorization processes are transparent and do not place undue burdens on clinicians and patients to ensure timely and equitable access to therapies for T2DM.***

During the policy roundtable, patients and clinicians described the burden of unknown out-of-pocket requirements and burdensome prior authorization and the resulting impact of both on patients. Patients described feeling exhausted and humiliated to be prescribed drugs that they discover at the pharmacy to be beyond their ability to afford. Clinical experts gave examples of onerous prior authorization criteria and/or processes that discourage clinicians from offering newer, more expensive, but potentially more beneficial drugs (e.g., drugs with cardiovascular benefit) equitably to all patients. This causes unacceptable harm to patients. This is a problem that

is fixable but requires the full commitment of multiple stakeholders working together to achieve more timely, equitable, and affordable drug access.

Federal and state policymakers should take the following actions:

- Work with payers to develop policies around interchangeability that allow pharmacists to exchange rejected drugs for covered drugs in the same class without having to go back to the prescribing clinician for approval, similar to substituting generic drugs for brand name drugs. This would potentially decrease the number of times a patient needs to go to the pharmacy, improve access and affordability of drugs, and decrease paperwork burden for clinicians.

Payers and health systems should take the following actions:

- Work with federal and state policymakers on interchangeability rules as described above.
- Work together to develop technologies to assist clinicians at the point of care know which drugs are covered and at what out-of-pocket cost for individual patients. These “cheat sheets” for clinicians could be electronic or paper but should be easily accessible at the point of care, e.g., deployed within the electronic medical record. An example of a web- and paper-based resource to improve prescriber knowledge about insurance coverage of common drugs is The Prescribing Guide for Hawaii (<https://www.prescribingguide.com/>).<sup>73</sup>

## Payers

### *Recommendation 1*

**For coverage purposes, it is not unreasonable for payers to consider tirzepatide as a separate class of T2DM therapy or as part of the GLP-1 RA class.**

Based on the 2022 American Diabetes Association (ADA) Standards of Medical Care for Diabetes, GLP-1 RAs with proven cardiovascular benefit (e.g., injectable semaglutide) are the recommended first- or second-line agent for patients with T2DM and at high risk for or with established ASCVD.<sup>4</sup> Although tirzepatide offers the additional GIP receptor agonist mechanism of action, which may have synergistic effects with GLP-1, clinical experts stated that it was not unreasonable to consider tirzepatide as part of the GLP-1 RA class, particularly before confirmation of cardiovascular benefit. However, clinical experts and patients value the apparent greater glucose lowering and weight loss potential of tirzepatide, and expect that cardiovascular benefit is likely to be confirmed based on data from tirzepatide's cardiovascular safety trial and its inclusion of GLP-1 receptor agonism as part of its mechanism of action. Thus, tirzepatide may also be considered separately from other GLP-1 RAs in terms of coverage criteria, access, and formulary tier placement.

### *Recommendation 2*

**Payers should consider broadening criteria for coverage of both GLP-1 RAs and SGLT-2 inhibitors since, based on the most current clinical guidelines, these drugs may be considered first-line therapy in T2DM patients with cardiovascular or renal disease, and wider use should be encouraged in these specific populations.**

Metformin is commonly used as first-line therapy based on its inexpensive cost and excellent safety profile. However, the most [recent ADA guidelines](#) suggest that use of GLP-1 RAs and SGLT-2 inhibitors with confirmed cardiovascular or renal benefit as initial therapy may be considered in patients at high risk for or with established ASCVD, CKD, or heart failure, regardless of HbA1c or use of metformin.<sup>4</sup> Some clinical experts have interpreted this recommendation to mean that for certain patients, initiation of drug therapy for T2DM can begin with a GLP-1 RA or SGLT-2 inhibitor, without preceding or concomitant use of metformin. Although clinical experts advised that it is not unreasonable to continue to require metformin use as first line and institute a HbA1c threshold for adding further therapy, in light of the new guidelines, health plans may also consider removing metformin as required step therapy, especially for patients at high risk for or with established ASCVD, CKD, or heart failure.

## ***Cost Sharing***

- Patient cost sharing should be based on the net price to the plan sponsor, not the unnegotiated list price.
- If all drugs in a drug class are priced so that they represent a fair value, it remains reasonable for payers to use preferential formulary placement with tiered cost sharing to help achieve lower overall costs.

## ***Coverage Criteria: General***

- Payers should offer alternatives to prior authorization protocols such as programs that give feedback on prescribing patterns to clinicians or exempt them from prior authorization requirements (“gold carding”) if they demonstrate high fidelity to evidence-based prescribing.
- Payers should document at least once annually that clinical eligibility criteria are based on high quality, up-to-date evidence, with input from clinicians with experience in the same or similar clinical specialty.
- Clinical eligibility criteria should be developed with explicit mechanisms that require payer staff to document using an open and transparent process that is readily accessible to the public that they have:
  - a) Considered limitations of evidence due to systemic under-representation of minority populations; and
  - b) Sought input from clinical experts on whether there are distinctive benefits and harms of treatment that may arise for biological, cultural, or social reasons across different communities; and
  - c) Confirmed that clinical eligibility criteria have not gone beyond reasonable use of clinical trial inclusion/exclusion criteria to interpret or narrow the FDA label language in a way that disadvantages patients with underlying disabilities unrelated to the condition being treated.

## ***Drug-Specific Considerations***

The large number of patients with T2DM, combined with the high annual prices for newer generation treatments, will lead payers to develop prior authorization criteria for tirzepatide and to consider other limits on utilization. Perspectives on specific elements of cost sharing and coverage criteria within insurance coverage policy are discussed below. Relevant [Fair Access Design Criteria](#) set out in ICER’s previous work are included.

None of these coverage terms, however, should undermine the tenets of fair access to which all patients have a fundamental right. To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might

appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for tirzepatide.

### ***Coverage Criteria***

- **Age:** Tirzepatide will likely be covered for adult patients with T2DM, in line with clinical trial eligibility criteria.
- **Clinical eligibility:** Clinical trials enrolled T2DM patients with HbA1c between 7% and 10.5%. Updated treatment guidelines from the American Diabetes Association emphasize that treatment with GLP-1 RA and SGLT-2 inhibitor class drugs may be considered independent of HbA1c targets and metformin use in patients with cardiovascular disease, chronic kidney disease, and heart failure given the demonstrated benefits of agents in those two classes on cardiovascular and renal outcomes.<sup>4</sup> However, the cardiovascular and renal benefits of GLP-1 RAs may not be a class effect.<sup>74</sup> Thus, because tirzepatide does not yet have confirmed cardiovascular benefit, it is not unreasonable for payers to consider requiring HbA1c to be above 7% on at least metformin therapy for coverage of tirzepatide. On the other hand, clinical experts also advised that given the level of HbA1c lowering and weight loss that tirzepatide provides, payers should also consider broadening eligibility criteria to include patients with HbA1c lower than 7%.
- **Exclusion criteria:** Clinical experts advised that it was not unreasonable to exclude patients who are on concomitant GLP-1 RA therapy, given the overlap in mechanism between GLP-1 RAs and tirzepatide.
- **Duration of coverage and renewal criteria:** Clinical experts advised that it is not unreasonable for payers to consider a limited duration of coverage, after which clinicians would be asked to confirm clinical benefit, particularly prior to confirmation of potential cardiovascular benefits of tirzepatide. However, the mechanism of action of the drug should pose no risk to having uninterrupted coverage.
- **Provider restrictions:** Given the prevalence of T2DM and that much of diabetes care occurs in primary care, there should be no restrictions on type of provider prescribing tirzepatide to help foster equitable access to the drug.



## **Step Therapy**

***Payers should only use step therapy when it provides adequate flexibility to meet the needs of diverse patients and when implementation can meet high standards of transparency and efficiency.***

Clinical experts and patient representatives stated that delayed and restricted access to treatment due to step therapy requirements for patients with T2DM is common, particularly for newer agents like GLP-1 RAs. While it is possible to tailor step therapy in a clinically responsible fashion, it is often administered with documentation burdens and inadequate procedures for exceptions that make step therapy a source of great frustration and the cause of poor outcomes for some patients due to the discontinuation of medicine/missed doses. A particular area of concern raised by patients involved requirements to re-step through previously failed therapies when insurance changed.

***New clinical guidelines suggest that metformin may no longer be the preferred first step in therapy for T2DM patients at high risk of or with established ASCVD, chronic kidney disease, or heart failure, and payers should consider access to drugs with proven cardiovascular or renal benefit without requiring a trial of metformin therapy. Payers who do establish step therapy with metformin should allow patients and clinicians to choose from options in both GLP-1 RA and SGLT-2 inhibitor classes as the next step.***

As stated above, the most current ADA guidelines state that for patients with T2DM who also have ASCVD, CKD or heart failure, metformin therapy is not necessarily a prerequisite to starting a GLP-1 RA or SGLT-2 inhibitor “with confirmed cardiovascular or renal benefit.”<sup>4</sup> The guidelines further subdivide those populations into patients at high risk of or with established ASCVD, where a GLP-1 RA drug is preferred, and patients with CKD or heart failure, where a SGLT-2 inhibitor is preferred, though both classes of agents can be used in all three populations. Thus, clinicians and patients should have the ability to choose the most appropriate drug(s) from these two classes.

Furthermore, in many cases, patients will need to be on a drug from both classes in order to reach their glycemic target, and thus access to both classes should be preserved for these populations. Since tirzepatide’s cardiovascular outcome data is not mature, health plans may choose to consider tirzepatide as part of the GLP-1 RA class due to its similarity in mechanism or as a separate class.

## Manufacturers

### ***Recommendation 1***

***Manufacturers should seek to set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of these new interventions for T2DM, while HbA1c lowering remains an important intermediate outcome, there is increasing emphasis on other potential benefits, including weight loss and prevention of complications such as cardiovascular events and kidney disease. Manufacturer pricing at launch should reflect these considerations and whether longer-term cardiovascular and renal outcomes have been demonstrated.***

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful. This is of particular concern in T2DM, as the financial burden is not only related to drug costs but also costs for glucose monitoring and the costs of managing the micro- and macrovascular complications that result from the disease.

Manufacturers should therefore price novel treatments in accordance with the demonstrated benefits to patients. In settings of substantial uncertainty, initial pricing should err on the side of being more affordable. This would allow more patients access, generating additional data on the real-world effectiveness of novel treatments that could be used in future assessment updates. In the case of tirzepatide, although it has substantial impact on HbA1c and weight, it does not yet have demonstrated cardiovascular or renal benefits that many GLP-1 RAs and SGLT-2 inhibitors have. Thus, launch pricing should reflect this uncertainty; if benefit is shown after the completion of the cardiovascular outcomes trial, the manufacturer should be allowed to adjust pricing in accordance with this benefit.

### ***Recommendation 2***

***Manufacturers should take steps to increase the diversity of participants in their clinical trials for T2DM. Given the high overall prevalence of T2DM in the US and the higher prevalence in minority populations, it is unacceptable that clinical trials still largely consisted of non-Hispanic white participants.***

African Americans, Hispanic Americans, Asian Americans, and Native American/Alaska Natives all have a higher prevalence of T2DM compared with non-Hispanic white Americans.<sup>1</sup> ICER's Health Improvement Distribution Index (HIDI) demonstrates that minority populations may have the opportunity for 10% to 40% more impact from an effective therapy than the general US population. However, the clinical trials for tirzepatide lacked racial and ethnic diversity, and thus any differential impact of tirzepatide – either in efficacy or harms – in these populations is not known.

Manufacturers need to fully commit to increase recruitment of minority populations in clinical trials and should work with patient groups and clinicians to design effective programs for the recruitment and retention of minority participants.

### **Recommendation 3**

***Manufacturers should not take steps to delay or deny the role of generic medications in improving the affordability of T2DM drugs.***

Because of their superior cardiovascular and renal outcomes, as well as their impact on weight, GLP-1 RAs and SGLT-2 inhibitors have risen to be the preferred first- or second-line drugs for the treatment of T2DM for many patients. Currently none of the GLP-1 RAs and SGLT-2 inhibitors with cardiovascular or renal benefit is available as a generic medication. As the patents expire for these drugs in the coming years, manufacturers should not prevent the timely development and marketing of generic versions of these drugs to improve access and affordability to these important medications.

## **Clinicians and Clinical Societies**

### **Recommendation 1**

***Clinical specialty societies should develop and disseminate programs to educate physicians who care for T2DM on the evolving treatment landscape, including the heightened importance of assessing for cardiovascular and renal comorbidities when choosing treatments.***

Given the number of comorbidities that T2DM patients have or develop, multiple clinicians – including primary care physicians and specialists – are likely to be involved in the care of T2DM patients. The majority of care for T2DM patients occurs in the primary care setting, with endocrinologists managing less than 15% of T2DM patients nationally.<sup>75</sup> Cardiologists and nephrologists are also likely to be heavily involved in the management T2DM patients with cardiovascular or renal disease given how common these comorbidities are in this population.

Studies show that less than 10% of eligible patients have received treatment with a GLP-1 RA or SGLT-2 inhibitor.<sup>76,77</sup> Thus, there is ample opportunity for all clinicians who care for patients with T2DM with cardiovascular or renal disease to consider recommending initiation of a GLP-1 RA or SGLT-2 inhibitor regardless of HbA1c, in line with the most recent clinical guidelines. However, barriers to prescribing these drugs include unfamiliarity or lack of experience prescribing these drugs, and for specialists, a feeling that management of T2DM is the responsibility of primary care physicians.<sup>78</sup>

Clinical societies should develop and disseminate programs to educate physicians caring for T2DM patients to identify patients who may be candidates for treatment with drugs having cardiovascular

or renal benefit such as GLP-1 RAs and SGLT-2 inhibitors. In particular, such programs should encourage team-based care with primary care physicians and specialists collaborating to ensure that patients are receiving evidence-based care with regard to management of both glucose and cardiometabolic risk factors.

## Researchers

### ***Recommendation 1***

***Clinical trials should be targeted to address gaps in knowledge about the comparative clinical effectiveness of GLP-1 RAs and SGLT-2 inhibitors and their use in patients without established ASCVD, CKD, or heart failure.***

Although cardiovascular and renal benefit from treatment with GLP-1 RAs and SGLT-2 inhibitors has been demonstrated in patients at high risk for or with established ASCVD, CKD, or heart failure, independent of their glucose-lowering effect, their impact on cardiovascular and renal outcomes in T2DM patients without those comorbidities is less certain. Furthermore, in patients without a strong indication for either class of medication but who require additional glucose-lowering, the order of stepwise therapy is not readily apparent. We did not find any head-to-head trials of GLP-1 RAs compared with SGLT-2 inhibitors and did not find any cardiovascular outcomes trials in patients without ASCVD. Thus, additional data, either from randomized clinical trials or high-quality observational studies could be useful in further guiding and personalizing therapy.

### ***Recommendation 2***

***More research is needed to generate quality-of-life data and data for use in economic evaluations regarding the societal costs of diabetes.***

Trials of treatments for T2DM should not only include intermediate outcomes such as HbA1c and weight and measures of potential micro- and macrovascular benefit but also collect data on quality of life of patients with T2DM. As the number of treatment choices increase and personalization of therapy is encouraged, the impact of a particular therapy on a patient's quality of life is an important factor to consider. Eli Lilly's inclusion of several validated quality-of-life measures, including versions of the Diabetes Treatment Satisfaction Questionnaire and EQ-5D are to be commended and should be replicated by all manufacturers when designing trials testing new therapies to treat T2DM.

We found there was a lack of comprehensive data to adapt for use in an economic evaluation regarding the societal costs of diabetes. These societal costs generally include costs to the patient and/or their caregivers outside of the health care sector. For example, the societal costs of

diabetes would capture the impact of diabetes on productivity loss (specifically, the average number of hours of presenteeism or absenteeism at work for patients or caregivers), as well as the amount and cost of informal care required for the patient. For use in an economic model, it would be particularly useful if the aforementioned costs were stratified by patient characteristics, such as age, race, and years since diagnosis. Importantly for diabetes, societal costs specific to diabetes-related complications, such as cardiovascular and renal events, are important for accurate economic modeling of the societal perspective.

### ***Recommendation 3***

***Research in T2DM should focus not only on interventions to treat the disease, but also include testing of upstream interventions to prevent onset of the disease.***

Given that some risk factors for developing diabetes, such as obesity, are modifiable with lifestyle interventions, data on the most effective types of structured lifestyle interventions for prevention and/or treatment are needed to help guide patients and clinicians. Such information could also be useful for policymakers in helping to guide funding for scaling up of effective prevention programs such as the Diabetes Prevention Program to ensure a wide reach and potentially decrease health inequities in access to such programs. Currently, we note that no health plans require participation in structured lifestyle intervention programs to treat diabetes prior to and/or concomitant with drug treatment for T2DM, despite clinical guidelines citing this as the backbone of diabetes treatment. With evidence of efficacy, health plans could be encouraged to cover structured lifestyle interventions in addition to drug therapy to ensure that T2DM patients receive comprehensive, evidence-based treatment.

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## Supplemental Materials



# A. Background: Supplemental Information

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## A1. Definitions

**Diagnosis of Type 2 Diabetes Mellitus (T2DM):** T2DM is characterized by progressive loss of adequate insulin secretion by pancreatic beta cells, frequently on the background of insulin resistance.<sup>79</sup> The diagnosis is made if any of the following criteria are met: (a) fasting plasma glucose  $\geq 126$  mg/dL; (b) 2-hour post-prandial glucose  $\geq 200$  mg/dL during 75-gram oral glucose tolerance test; (c) HbA1c  $\geq 6.5\%$ ; or (d) random plasma glucose  $\geq 200$  mg/dL and symptoms of hyperglycemia.<sup>80</sup>

**Glycated Hemoglobin (HbA1c):** Blood test that measures the amount of glycated red blood cells in the blood. It reflects average blood sugar levels over the past 2-3 months and increases as the amount of glucose increases in the blood. Patients with HbA1c  $\geq 6.5\%$  are considered to have diabetes.<sup>80</sup>

**Microvascular complications:** Persistent exposure to high levels of blood glucose can lead to damage to small blood vessels in the eyes, kidney, and nerves.

- Retinopathy (eye): Most common microvascular complication, causing around 10,000 new cases of blindness each year in the US.<sup>11</sup> Most cases develop within 7-20 years after diagnosis.<sup>81</sup>
- Nephropathy (kidney): Leading cause of renal failure in the US, can be present at diagnosis.<sup>11,82</sup> Characterized by elevated levels of protein in the urine and/or decreased estimated glomerular filtration rate (eGFR).<sup>82</sup>
- Neuropathy (nerves): Characterized by symptoms or signs of peripheral nerve dysfunction (e.g., burning, tingling, numbness, sensory loss to light touch, vibration or temperature, autonomic dysfunction) in people with diabetes, after excluding other causes.<sup>82</sup> Can lead to foot ulcers, injury from falls, and ultimately limb amputation.<sup>11</sup>

**Macrovascular complications:** Diseases characterized by atherosclerosis, including coronary artery disease and cerebrovascular disease. Patients with T2DM have a much higher risk of cardiovascular events such as myocardial infarction or stroke, and cardiovascular death is the most common cause of death in patients with diabetes.<sup>11</sup>



**Cardiovascular Outcomes Trial (CVOT):** Long-term, prospective trials of diabetes drugs specifically examining cardiovascular safety. CVOTs became required by the FDA in 2008 for the approval of new diabetes drugs due to cardiovascular safety concerns raised by rosiglitazone, a thiazolidinedione.<sup>28</sup> Trial results must demonstrate that the upper bound of the 95% confidence interval of the hazard ratio for cardiovascular events is less than 1.8 for a drug to be considered safe from a cardiovascular perspective. CVOTs have been conducted for newer diabetes drugs, including DPP-4 inhibitors, GLP-1 RA, and SGLT-2 inhibitors.

**Atherosclerotic Cardiovascular Disease (ASCVD):** Disease of the arteries caused by plaque buildup in artery walls. ASCVD includes the clinical conditions of coronary artery disease, acute coronary syndromes, stroke, transient ischemic attack, peripheral vascular disease, coronary or other arterial revascularization, and aortic aneurysm.<sup>83</sup> Patients with diabetes are at higher than normal risk for ASCVD.<sup>84</sup>

**Major Adverse Cardiovascular Events (MACE):** The major causes of morbidity and death in patients with ASCVD, and an often-used endpoint in clinical trials. There is no standard definition of MACE, but in general it can include: fatal and non-fatal myocardial infarction, heart failure, recurrent angina pain, repeat hospitalization for cardiovascular-related illness, repeat percutaneous coronary intervention, coronary bypass surgery, fatal and non-fatal stroke, and all-cause mortality.<sup>85</sup> For diabetes drugs, 3-point MACE (MACE-3) is often used as an endpoint in CVOT, including non-fatal myocardial infarction (may or may not include silent infarction), non-fatal stroke, and cardiovascular mortality.

**Congestive Heart Failure:** A chronic condition where the heart does not pump enough blood for the body's needs, leading to inadequate blood flow to vital organs (e.g., kidneys) and buildup of fluid in other organs (e.g., lungs). This can happen when the heart muscle is weakened or is too stiff. The most common symptoms of heart failure are shortness of breath, leg swelling, and fatigue.

**Chronic kidney disease (CKD):** A chronic condition where kidney function is decreased, resulting in buildup of waste and fluid in the body. It is defined as a reduction in eGFR to 60 mL/min/1.73 m<sup>2</sup> or less and/or the presence of protein in the urine. Symptoms of CKD often do not occur until the advanced stages, and can include edema, loss of appetite, nausea, fatigue, high blood pressure, anemia, high potassium, and bone disease. Diabetes is the leading cause of CKD in the US.<sup>11</sup>

**Short Form (36) Health Survey (SF-36):** A 36-item self-reported questionnaire of health-related quality of life. It includes questions about general health, activity limitations, physical and emotional health, social activities, and pain.<sup>86</sup> It is often used as a quality-of-life measure in clinical trials and is not specific to any health condition.

**Diabetes Treatment Satisfaction Questionnaire (DTSQ):** An 8-item self-reported questionnaire of psychological well-being (depression, anxiety, and positive well-being) and treatment satisfaction in

patients with T2DM.<sup>24</sup> It is widely used in clinical trials to assess the impact of diabetes interventions on quality of life.

**Impact of Weight on Quality-of-Life Questionnaire:** A 74-item self-reported questionnaire assessing the effects of obesity on health-related quality of life. The scale measures the impact of obesity on physical function, self-esteem, sexual life, public distress, and work.<sup>87</sup>

**Continuous Glucose Monitor (CGM):** A non-invasive device that measures interstitial blood glucose levels constantly through skin sensors, providing real-time information about blood glucose levels. Use of CGMs can result in better glycemic control compared with regular blood glucose monitoring in patients with T2DM on insulin therapy.<sup>88,89</sup>

**Health Improvement Distribution Index:** The Health Improvement Distribution Index identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The Health Improvement Distribution Index is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if the disease prevalence was 10% in poor Americans whereas the disease prevalence across all Americans was 4%, then the Health Improvement Distribution Index would be  $10\%/4\% = 2.5$ . For interventions known to increase health in this disease and that accomplish equal access across the entire population, poor Americans would receive 2.5 times the health improvements as compared to the same sized group of Americans without regard to economic status. Health Improvement Distribution Indexes above one suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. This statistic may be helpful in characterizing a treatment's contextual considerations and potential other benefits ([Section 5](#)).

For this calculation, we used data from the Centers for Disease Control 2020 National Diabetes Statistics Report.<sup>1</sup> We used the overall US population prevalence of diagnosed diabetes, 10.2%, as the denominator. We performed calculations for the following subgroups\*:

- American Indian/Alaska Native:  $14.7\%/10.2\% = 1.4$
- Asian Indian:  $12.6\%/10.2\% = 1.2$
- Hispanic:  $12.5\%/10.2\% = 1.2$
- Non-Hispanic Black:  $11.7\%/10.2\% = 1.1$

\*ICER acknowledges the sensitivities around the naming conventions of these racial and ethnic categories, and for the purposes of the Health Improvement Distribution Index, we attributed these based on the populations analyzed in the 2020 National Diabetes Statistics Report published by the Centers for Disease Control and Prevention.<sup>1</sup>

## A2. Drug Classes for the Treatment of Type 2 Diabetes

**Metformin:** An orally administered biguanide that decreases glucose production and absorption and improves insulin sensitivity. It is recommended as initial pharmacotherapy for most patients with T2DM due to its efficacy and favorable safety profile.<sup>4</sup> It decreases HbA1c by 1.1% on average without significant risk of hypoglycemia. Additionally, it is associated with modest weight loss and may improve cardiovascular outcomes, though there are no direct cardiovascular outcomes trials.<sup>23</sup> Side effects from metformin are mainly gastrointestinal; there is also a rare risk of lactic acidosis, and the drug should be discontinued in patients with severe chronic kidney disease. Metformin is recommended to be continued as long as it is tolerated and not contraindicated.<sup>4</sup>

**Sulfonylureas (SU):** Oral hypoglycemic agents such as glyburide and glipizide that increase insulin secretion by stimulating pancreatic beta cells. They lower HbA1c by 1-2%. The most common side effects are hypoglycemia and weight gain. Sulfonylureas may be associated with progressive dysfunction of pancreatic beta cells and worsening diabetes control in the long-term. Sulfonylureas do not appear to have an impact on cardiovascular outcomes.<sup>90</sup>

**Thiazolidinediones (TZD):** Oral hypoglycemic agents such as pioglitazone that lower blood glucose by decreasing insulin resistance and decreasing glucose production in the liver. TZDs lower HbA1c by around 1-1.25%<sup>91</sup>, and also have favorable effects on lipids and hepatic steatosis. TZDs have mixed cardiovascular data. Rosiglitazone has been associated with an increased risk of myocardial infarction<sup>92</sup>, however, pioglitazone has been shown to decrease fatal and non-fatal stroke in patients with previous strokes.<sup>93</sup> TZDs are also associated with weight gain and fluid retention, and an increased incidence of heart failure and heart failure hospitalizations.<sup>93,94</sup> There is also an increased risk of bone fractures with long-term use of TZDs.<sup>95</sup>

**Dipeptidyl peptidase-4 (DPP-4) inhibitors:** Oral hypoglycemic agents such as sitagliptin, saxagliptin, linagliptin, and alogliptin that lower blood glucose by inhibiting the activity of the DPP-4 enzyme in the plasma. Inhibition of DPP-4 stops degradation of incretins such as GLP-1 and GIP, which in turn increases insulin secretion and decreases gastric emptying.<sup>96</sup> DPP-4 inhibitors lower HbA1c on average by around 0.75%.<sup>97</sup> Hypoglycemia is rare, and they are considered weight neutral. However, DPP-4 inhibitors do not appear to impact cardiovascular outcomes.<sup>90</sup> Common side effects include runny nose, headache, and diarrhea. DPP-4 inhibitors have also been associated with more severe side effects such as severe joint pains, pancreatitis, angioedema, and Stevens-Johnson syndrome.

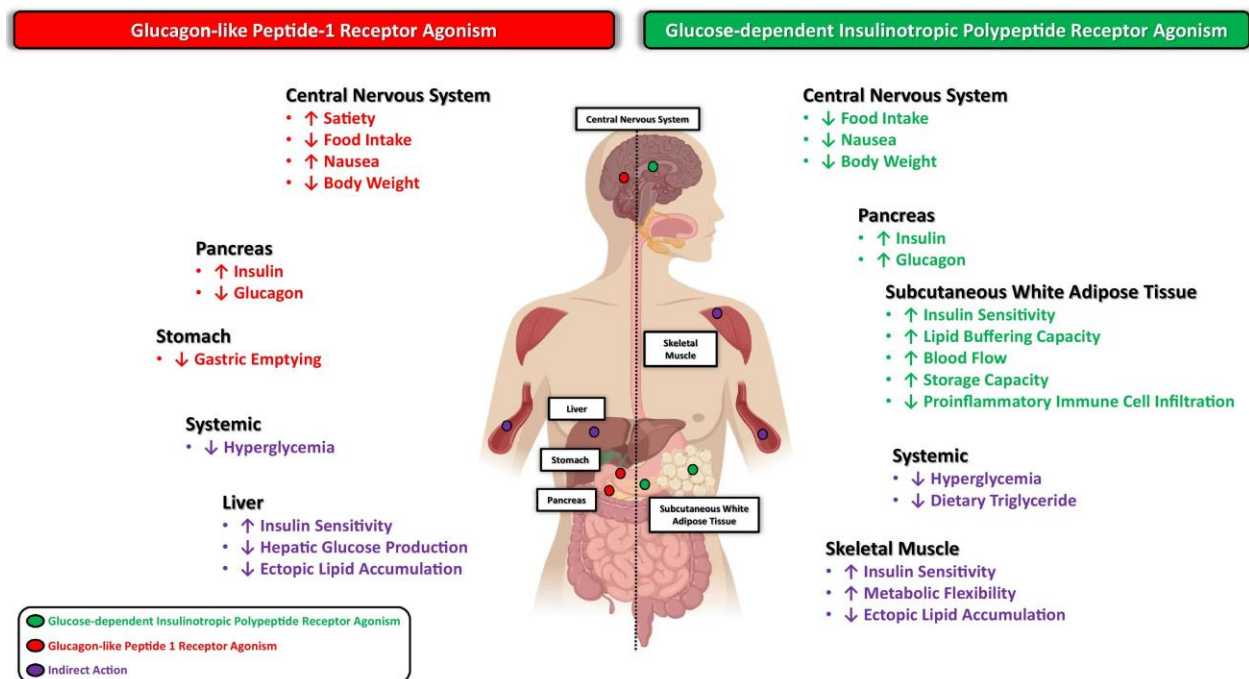
**Sodium-glucose co-transporter 2 (SGLT-2) inhibitors:** Oral hypoglycemic agents such as empagliflozin, canagliflozin, and dapagliflozin. SGLT-2 is a protein that is involved in the reabsorption of glucose filtered by the kidneys, and in patients with T2DM, SGLT-2 appears to be upregulated, increasing the rate of renal glucose reabsorption. SGLT-2 inhibitors block glucose reabsorption, resulting in loss of glucose in the urine. As add-on therapy to metformin and/or sulfonylureas, SGLT-2 inhibitors lowered HbA1c by up to an additional 1%. Hypoglycemia is rare with SGLT-2 inhibitors and modest weight loss has been observed. SGLT-2 inhibitors have been shown to reduce cardiovascular events, particularly hospitalization for heart failure and kidney disease.<sup>98</sup> Side effects of SGLT-2 inhibitors include dehydration, urinary tract infections, genital

yeast infections, acute kidney injury and increased LDL-C. More severe side effects such as urosepsis and ketoacidosis have also been noted, as well as an association with increased diabetic foot amputations.<sup>99</sup>

**GLP-1 receptor agonists (GLP-1 RA):** Oral and injectable hypoglycemic agents such as semaglutide (has both oral and injectable forms), dulaglutide, exenatide, and liraglutide. GLP-1 is an incretin that stimulates release of insulin from pancreatic beta cells in response to glucose. It has also been shown to slow gastric emptying, reduce food intake, and inhibit inappropriate post-meal glucagon release (Figure A1).<sup>100</sup> Injectable GLP-1 RAs can be administered twice daily, daily or weekly; oral semaglutide is taken daily. GLP-1 RAs have been shown to lower HbA1c (0.8-1.6%), weight (1-3 kg), blood pressure and lipids. Additionally, cardiovascular outcomes trials have demonstrated cardiovascular and renal benefits for some GLP-1 RAs.<sup>7</sup> The most prominent side effects are gastrointestinal, and hypoglycemia is rare. There is a risk of developing thyroid C-tumors, though this has not been seen in clinical practice.<sup>101</sup>

**Glucose-dependent insulintropic polypeptide/GLP-1 receptor agonist (GIP/GLP-1 RA):** Dual agonist targeting two incretins, GIP and GLP-1, both of which are released after meals to facilitate insulin secretion. Tirzepatide, an injectable agent, is currently the only member of this class. The dual receptor agonism leads to a decrease in blood sugar through an increase in insulin secretion and increase in insulin sensitivity in the liver and skeletal muscles. Both GLP-1 and GIP have additional impacts on other tissues, as depicted in Figure A1. For example, both GLP-1 and GIP mediate weight loss through effects on satiety centers in the central nervous system. GLP-1 RA additionally decreases gastric emptying, and GIP has impacts on the subcutaneous white adipose tissue.<sup>100</sup>

**Figure A1. Pleiotropic Effects of Dual GIP Inhibition and GLP-1 Receptor Agonism in the Treatment of T2DM<sup>100</sup>**



Trends in Endocrinology & Metabolism

**Insulin:** Insulin is produced in pancreatic beta cells and controls the amount of blood glucose in the bloodstream, helps promote storage of glucose in the liver, adipose tissue, and muscles, and regulates metabolism of carbohydrates, fats, and proteins. There are short, intermediate, and long-acting insulins, delivered mainly by injection, which are used alone or in combination by patients with T2DM to help control blood sugar levels. The main side effects of insulin are hypoglycemia and weight gain.

### A3. Potential Cost-Saving Measures in Type 2 Diabetes

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see <https://icer.org/our-approach/methods-process/value-assessment-framework/>). These services are ones that would not be directly affected by therapies for T2DM (e.g., reduction in disability), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of T2DM beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with T2DM that could be reduced, eliminated, or made more efficient. No suggestions were received.

## B. Patient Perspectives: Supplemental Information

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### **B1. Methods**

ICER engaged with individual patients, patient groups, including representatives from diabetes and kidney disease advocacy organizations, and clinical experts to gather information to better understand patient experiences with T2DM. In total, we spoke with five individual patients and seven advocacy organizations via focus groups and conference calls. We also spoke with three clinical experts throughout the review process. We also reviewed research literature suggested by or provided to ICER by advocacy organizations.

Patients and advocacy groups provided information on the impact of T2DM on patients throughout the disease course, particularly concerning aspects of the disease and caregiving that are not well-reflected in the current literature. These organizations also assisted with literature review to find information that was considered for inputs into the economic model.

## C. Clinical Guidelines

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Clinical practice guidelines for the treatment of T2DM have been issued by several US and non-US-based organizations. These guidelines are summarized below.

### ***The American Diabetes Association (ADA)<sup>3,4,102</sup>***

The ADA's Standards of Medical Care in Diabetes guidelines are updated yearly and include recommendations on diagnosis and treatment of T2DM and its complications.<sup>102</sup> The 2022 guideline update states that first-line treatment should consider patient-specific factors, including comorbidities, risk of hypoglycemia, risk of side effects, cost and access considerations, impact on patient weight, along with patient preferences. A recommended HbA1c target is less than 7.0% for most nonpregnant adults, although a patients' individualized target HbA1c may be lower if it can be safely achieved without significant hypoglycemia or adverse effects, or higher (e.g., <8.0%) in patients with limited life expectancy or in whom treatment harms outweigh benefits.<sup>3</sup>

For most patients, initial therapy will generally include metformin and comprehensive lifestyle modifications (e.g., healthy eating patterns, medical nutrition therapy, regular physical activity, weight management, smoking cessation).<sup>4</sup> If a patient does not have chronic kidney disease (CKD), atherosclerotic cardiovascular disease (ASCVD), or concerns regarding weight management, and the HbA1c target is not achieved after three months of therapy, it is recommended to have a combination of metformin and any of six preferred medication classes which include basal insulin, DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors, sulfonylureas, or thiazolidinediones, dependent upon patient factors and drug-specific effects (Figure C1.). For example, if there is a compelling need to either minimize weight gain or help promote weight loss, use of either GLP-1 RAs or SGLT-2 inhibitors are preferred.

For T2DM patients who also have established ASCVD or multiple ASCVD risk factors, use of either SGLT-2 inhibitors or GLP-1 RAs are recommended to be considered as initial therapy, regardless of HbA1c or metformin use (Figure C1.). Among T2DM patients who have established ASCVD and heart failure or are at high risk of developing heart failure, or have established CKD, use of SGLT-2 inhibitors is preferred, regardless of HbA1c or metformin use (Figure C1.).



Figure C1. 2022 ADA Recommendations for Pharmacologic Treatment for Adults with T2DM<sup>4</sup>

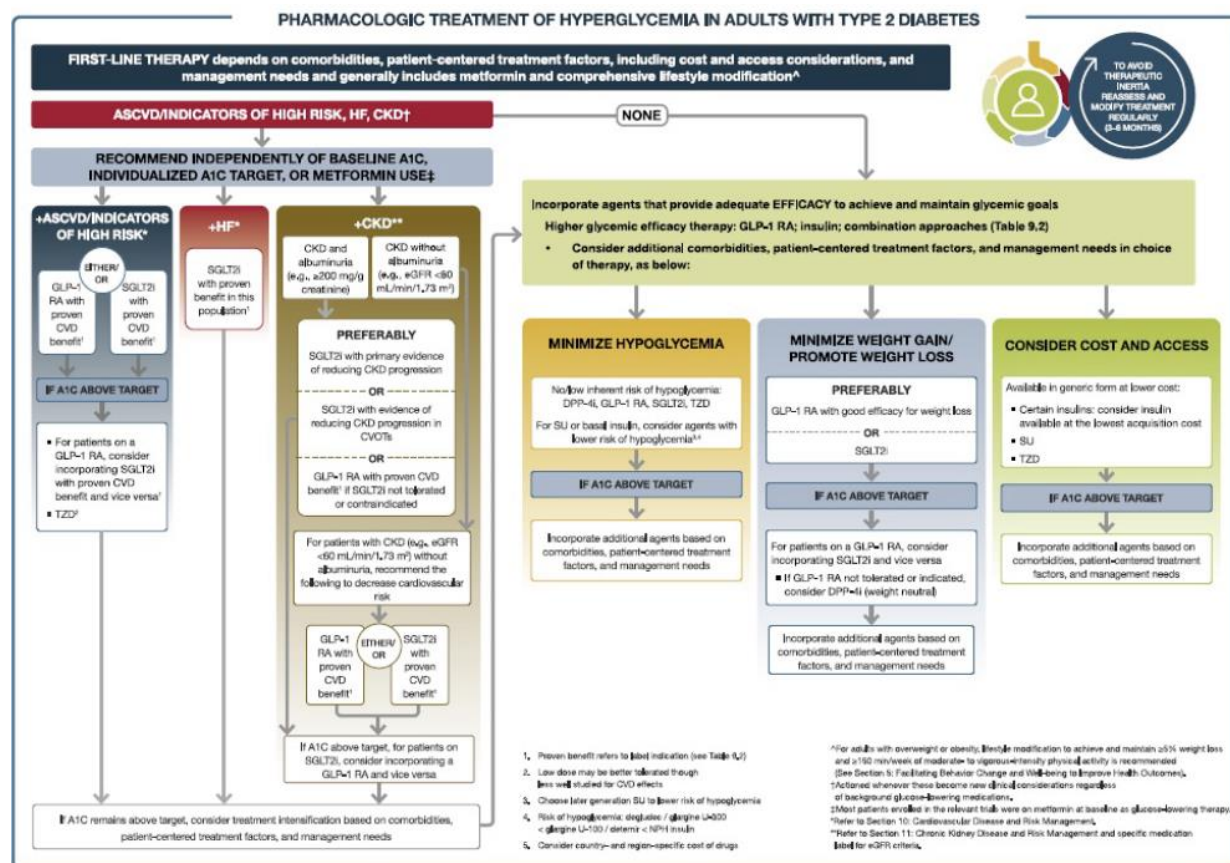


Figure 9.3—Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (43) and Buse et al. (44). For appropriate context, see Fig. 4.1. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered treatment factors, and management needs. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVDs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, type 2 diabetes; TZD, thiazolidinedione.

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## American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE)<sup>103</sup>

The AACE and ACE published a Comprehensive Type 2 Diabetes Management Algorithm in 2019. The guidelines recommend that in addition to promoting lifestyle optimization measures, clinicians should individualize both glycemic targets and choice of therapy. Choice of therapy should be patient-centered, consider ASCVD, heart failure, and CKD status, and achieved through shared decision-making. A HbA1c ≤6.5% is considered optimal if it can be achieved in a safe and affordable manner and glycemic therapy should be evaluated frequently (e.g., every 3 months) so that glycemic targets should be achieved as soon as possible. Continuous glucose monitoring is highly recommended to assist patients in reaching glycemic targets.

Choice of therapy is based on comorbidities and HbA1c status at initiation of therapy. For patients with established ASCVD or high risk of ASCVD, CKD stage 3, or heart failure with reduced ejection



fraction, a long-acting GLP-1 RA or SGLT-2 inhibitor with proven efficacy in these conditions is preferred. For patients with a HbA1c  $\geq 7.5\%$ -9.0% or HbA1c  $\geq 9.0\%$  without symptoms at initiation of therapy, dual therapy with metformin and another agent is recommended, with the addition of a third agent if glycemic control is not achieved within 3 months. For patients with a HbA1c  $> 9.0\%$  with symptoms, insulin with or without other agents is preferred.

***The European Society of Cardiology (ESC) and the European Association of the Study of Diabetes (EASD)<sup>104</sup>***

The ESC and EASD guidelines on diabetes, pre-diabetes, and CVD recommend the use of metformin along with lifestyle modifications (e.g., healthy eating patterns, regular physical activity, smoking cessation, weight management) as first-line therapy in patients with T2DM without established ASCVD or at high CV risk.<sup>104</sup> A recommended HbA1c target is less than 7.0% for most adults, however, target goals should be individualized on a per-patient basis.

For patients with T2DM and CVD or at high CV risk, the use of GLP-1 receptor agonists or SGLT-2 inhibitors are recommended to reduce the risk of CV events. For patients with T2DM and heart failure, SGLT-2 inhibitors are recommended to reduce the risk of hospitalization from heart failure. Saxagliptin is not recommended for use in patients with heart failure. For patients with T2DM and CKD, SGLT-2 inhibitors are recommended to reduce progression of CKD.

***National Institute for Health and Care Excellence (NICE)<sup>105</sup>***

NICE published guidelines for Type 2 diabetes in adults in 2015, and updated the guidelines in 2019. Along with evidence-based patient education delivered by trained educators, a personalized diabetes management plan including advice about diet, exercise, and weight loss, the NICE guideline recommends metformin as initial drug treatment. HbA1c targets should be individualized, based on risk of hypoglycemia (HbA1c  $\leq 6.5\%$  in patients who are not on drugs that cause hypoglycemia and  $\leq 7.0\%$  if patients are on drugs that cause hypoglycemia). HbA1c targets can be relaxed in patients for whom tight glucose control is not appropriate.

If metformin is not sufficient to achieve the glycemic target, the guidelines recommend dual therapy with the addition of a sulfonylurea, DPP-4 inhibitor, pioglitazone or SGLT-2 inhibitor. Triple therapy with metformin and two of the following: DPP-4 inhibitor, sulfonylurea, and/or pioglitazone, or starting insulin is recommended as a second intensification step. GLP-1 RAs are recommended only if metformin plus two other oral drugs is not effective, particularly in patients who are obese or have obesity-related complications, or have relative contraindications to insulin (e.g., patients in whom insulin therapy would have significant occupational implications).

# D. Comparative Clinical Effectiveness:

## Supplemental Information

### **D1. Detailed Methods**

#### **PICOTS**

##### ***Population***

Our intervention of interest for this review was injectable tirzepatide (Eli Lilly) added to background therapy (metformin +/- sulfonylureas or thiazolidinediones).

##### **Comparators**

We compared tirzepatide to background therapy and each of the following add-on agents:

- Semaglutide (Ozempic®, Novo Nordisk), an injectable GLP-1 receptor agonist
- Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), an oral SGLT-2 inhibitor

##### **Outcomes**

The outcomes of interest are described in the list below.

- Glycated hemoglobin (HbA1c) levels
- Fasting plasma glucose
- Body weight
- Waist circumference
- Blood pressure
- Percentage of patients achieving HbA1C targets of <7.0%, ≤6.5%, and/or <5.7%
- Lipid profile (e.g., Total Cholesterol, Low-Density Lipoprotein Cholesterol, High-Density Lipoprotein Cholesterol, and Triglycerides)
- Use of rescue medication (e.g., additional glucose-lowering medication)
- Health-related quality of life and activities of daily living (e.g., Diabetes Treatment Satisfaction Questionnaire (DTSQ), EuroQol 5-Dimensions Health-Related Quality of Life questionnaire (EQ-5D), Impact of Weight on Quality of Life Questionnaire–Lite (IWQOL-Lite), Short Form Health Survey (SF-36))
- Macrovascular outcomes including:
  - All-cause mortality
  - Cardiovascular mortality
  - Stroke

- Myocardial infarction
  - Heart failure requiring hospitalization or an urgent heart failure visit
- Microvascular outcomes including:
  - Retinopathy
  - Nephropathy
  - Neuropathy
- Adverse events including:
  - Hypoglycemia
  - Pancreatitis
  - Urogenital infections
  - Gastrointestinal effects
  - Fractures
  - Discontinuation (all-cause, due to adverse events)
  - Serious adverse events including death

### ***Timing***

Evidence on intervention effectiveness and harms was derived from studies of at least 3 months' duration.

### ***Settings***

All relevant settings were considered, with a focus on outpatient settings in the United States.

### ***Study Design***

Randomized controlled trials and non-randomized controlled trials with any sample size were included.

**Table D1.1 PRISMA 2009 Checklist**

|                                    |    | Checklist Items   |
|------------------------------------|----|---|
| TITLE                              |    |   |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.   |
| ABSTRACT                           |    |   |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. |
| INTRODUCTION                       |    |   |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.  |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  |
| METHODS                            |    |   |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.   |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.   |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.   |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).   |

|                               |    |  |
|-------------------------------|----|--|
| Synthesis of results          | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.                                       |
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).   |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.   |
| <b>RESULTS</b>                |    |  |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.   |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  |
| <b>DISCUSSION</b>             |    |  |
| Summary of evidence           | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).                    |
| Limitations                   | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  |
| Conclusions                   | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  |
| <b>FUNDING</b>                |    |  |
| Funding                       | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.   |

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for T2DM followed established best research methods.<sup>106,107</sup> We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>108</sup> The PRISMA guidelines include a checklist of 27 items, which are described further in Table D1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and Emtree terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see <https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/>). Where feasible and deemed necessary, we also accepted data submitted by manufacturers “in-confidence,” in accordance with ICER’s published guidelines on acceptance and use of such data (<https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/>).

**Table D1.2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, and EBM Reviews - Cochrane Central Register of Controlled Trials**

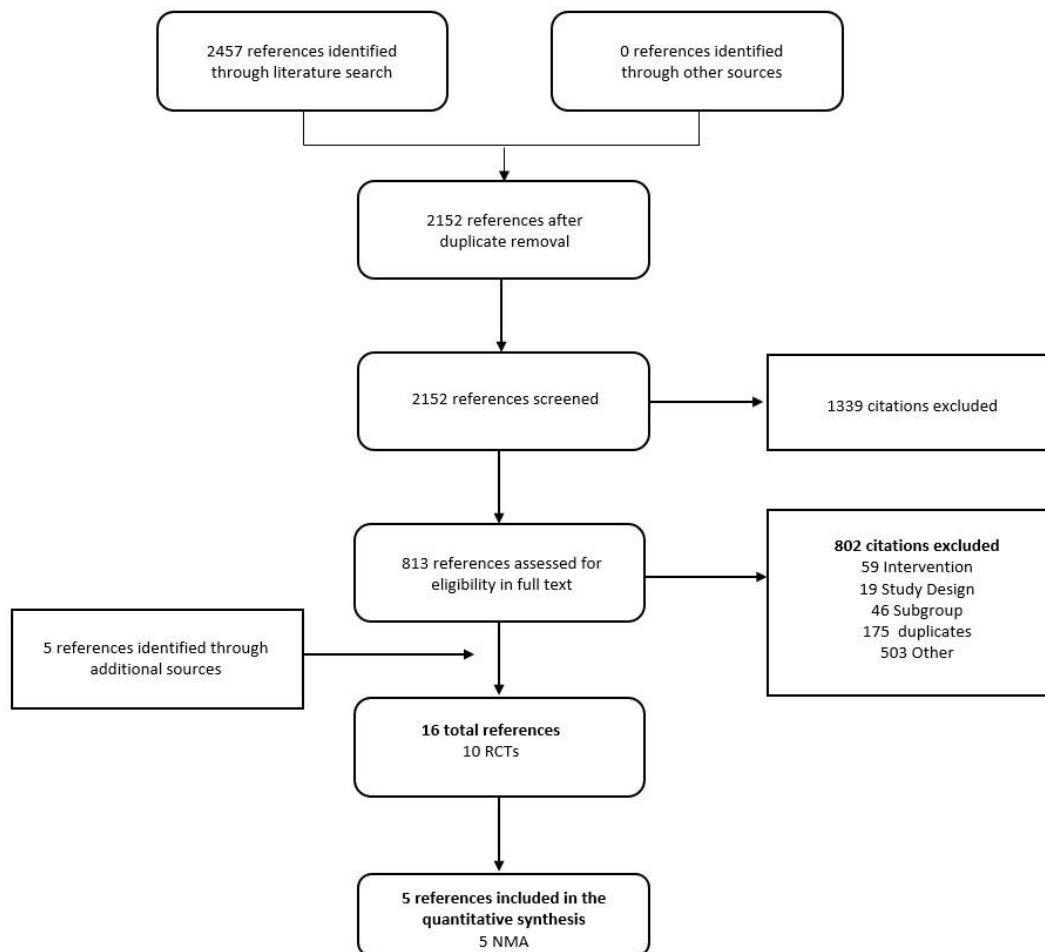
|           | Search Terms  |
|-----------|---|
| <b>1</b>  | exp Diabetes Mellitus, Type 2/  |
| <b>2</b>  | ((adult or ketosis-resistant or matur* or late or "non-insulin depend*" or "noninsulin depend*" or slow or stable or "type 2" or "type II" or lipoatrophic) adj3 diabet*) or T2D* or NIDDM).ti,ab.  |
| <b>3</b>  | 1 or 2  |
| <b>4</b>  | (tirzepatide or "LY3298176" or LY3298176).ti,ab.  |
| <b>5</b>  | (semaglutide or "nn 9535" or nn9535 or ozempic).ti,ab.  |
| <b>6</b>  | (empagliflozin or "BI 10773" or BI10773 or jardiance).ti,ab.  |
| <b>7</b>  | 4 or 5 or 6   |
| <b>8</b>  | 3 and 7   |
| <b>9</b>  | (address or autobiography or bibliography or biography or case reports or clinical trial phase i or comment or conference review or congress or consensus development conference or duplicate publication or dictionary or directory or editorial or guideline or interview or lecture or legal case or legislation or letter or meta analysis or news or newspaper article or note or patient education handout or periodical index or personal narrative or portrait or practice guideline or review or systematic review or video-audio media).pt. |
| <b>10</b> | conference abstract.pt.   |
| <b>11</b> | 8 not (9 or 10)   |
| <b>12</b> | (clinical and trial).ti,ab. or exp 'clinical trials as topic'/ or clinical trial.pt. or random*.ti,ab. or exp 'random allocation'/ or tu.xs   |
| <b>13</b> | 11 and 12   |
| <b>14</b> | limit 13 to english language  |
| <b>15</b> | (animals not (human and animals)).sh.   |
| <b>16</b> | 14 not 15   |
| <b>17</b> | remove duplicates from 16   |

**Table D1.3. Search Strategy of EMBASE SEARCH**

|    | Search Terms  |
|----|---|
| 1  | 'non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'  |
| 2  | ((('adult OR 'ketosis resistant' OR matur* OR late OR 'non-insulin depend*' OR 'noninsulin depend*' OR slow OR stable OR 'type 2' OR 'type ii' OR lipoatrophic) NEAR/3 diabet*):ti,ab) OR t2d*:ti,ab OR niddm:ti,ab   |
| 3  | #1 or #2  |
| 4  | 'tirzepatide'/exp   |
| 5  | 'tirzepatide':ti,ab OR 'LY3298176':ti,ab OR 'LY3298176':ti,ab   |
| 6  | 'semaglutide'/exp   |
| 7  | Semaglutide:ti,ab OR 'nn 9535':ti,ab OR 'nn9535':ti,ab OR 'ozempic':ti,ab   |
| 8  | 'empagliflozin'/exp   |
| 9  | empagliflozin:ti,ab OR bi10773:ti,ab OR 'bi 10773':ti,ab OR 'jardiance':ti,ab   |
| 10 | #4 OR #5 OR #6 OR #7 OR #8 OR #9  |
| 11 | #3 AND #10  |
| 12 | #11 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'in vitro study'/de OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'network meta-analysis'/de OR 'nonhuman'/de OR 'phase 1 clinical trial (topic)'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'systematic review'/de OR 'systematic review (topic)'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) |
| 13 | 'clinical':ti,ab AND 'trial':ti,ab OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk OR 'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp   |
| 14 | #12 AND #13   |
| 15 | #14 AND [english]/lim   |
| 16 | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp   |
| 17 | #15 NOT #16   |
| 18 | #17 NOT [medline]/lim   |



**Figure D1.1 PRISMA Flow Chart Showing Results of Literature Search for Tirzepatide for Type 2 Diabetes**



## Study Selection

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study. All literature that did not undergo a formal peer review process is described separately.

## ***Tirzepatide***

There are four tirzepatide trials, two Phase 2 trials that compare tirzepatide to background therapy and two Phase 3 trials that compare tirzepatide against injectable semaglutide and tirzepatide against insulin glargine.

## ***NMA Linkages***

A total of four references relating to four RCTs were used as linkages for the NMA. Two RCTs related to oral semaglutide, one RCT related to injectable semaglutide, and one RCT contained a placebo and sitagliptin arm.

## ***CVOTs***

A total of three references relating to two RCTs evaluating cardiovascular outcomes. One RCT reviewed empagliflozin and the second reviewed injectable semaglutide.

## **Data Extraction and Quality Assessment**

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories “good,” “fair,” or “poor” (see Table D4.1.).<sup>109</sup> Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

**Good:** *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

**Fair:** *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

**Poor:** *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

## Assessment of Level of Certainty in Evidence

We used the [ICER Evidence Rating Matrix](#) to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.<sup>110,111</sup>

## Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for tirzepatide, semaglutide, and empagliflozin using the clinicaltrials.gov database of trials. We searched for studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

## Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see [Section D4](#)) and synthesized qualitatively in the body of the review. In addition, we evaluated the comparative efficacy of tirzepatide, injectable semaglutide, empagliflozin, and background therapy by means of network meta-analysis (NMA), where feasible. Based on data availability, our NMA evaluated HbA1c, body weight, LDL, and SBP outcomes at 40 weeks. Network Meta-Analysis Supplemental Information below ([Section D2](#)) contains a detailed description of the NMA methods. Due to inconsistent or limited data reporting, other outcomes were only described narratively in the body of the report or in [Section D4](#) of the Report Supplement.

## D2. Network Meta-Analysis: Supplemental Information

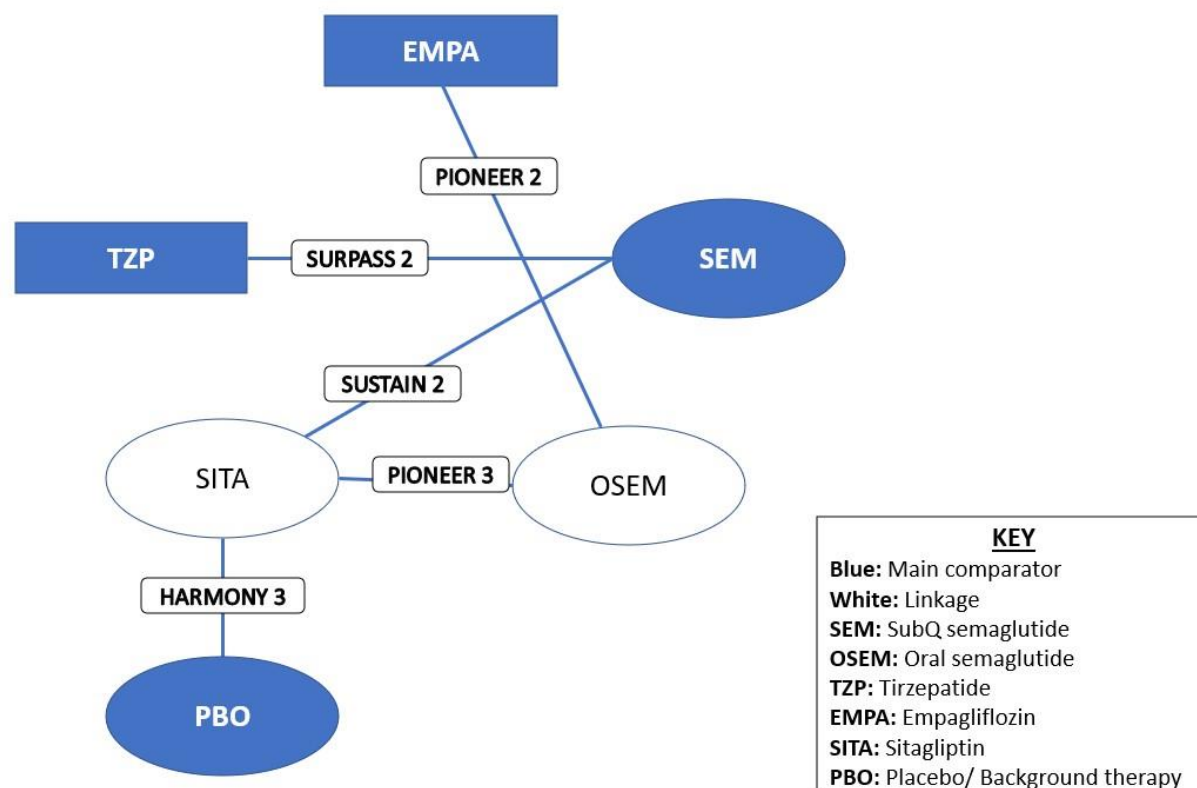
### *NMA Methods*

We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest. Trials deemed sufficiently similar in terms of population, intervention type, duration, and outcome definitions were included in the NMAs. Based on data availability, we developed quantitative, indirect comparisons of tirzepatide, injectable semaglutide, empagliflozin, and background therapy using a Bayesian NMA for outcomes of change in HbA1c, weight, LDL, and SBP at 40 weeks in adult patients with T2DM ([Figure D2.1](#)). The primary endpoints of the tirzepatide trial, SURPASS-2 was measured at 40 weeks, PIONEER-2 and 3 were measured at 52 weeks, SUSTAIN-2 at 56 weeks, and HARMONY-3 at 104 weeks. We received academic-in-confidence outcomes data at week 40 from manufacturers of four of the five trials in the NMA. We were

unable to access week 40 data from the HARMONY-3 trial. Thus, we used digitized estimates from published figures to calculate change in HbA1c and weight at week 40; we were limited to using change from baseline to week 104 for the LDL and SBP outcomes. For the outcomes of HbA1c and weight, results were reported using the treatment-regimen or equivalent estimand. For the outcome of LDL, results were reported using the efficacy estimand for SURPASS-2 and treatment-regimen estimand equivalent for SUSTAIN-2, PIONEER-2 and 3.

All four outcomes were analyzed as continuous outcomes using a generalized linear model with identity link (Tables D2.1.-2.3.). Vague priors were used for study-specific baselines and basic parameters in the Bayesian NMA models. However, between-study heterogeneity could not be precisely estimated in the random effect models with noninformative priors due to the small number of studies available. This was reflected by the wide credible intervals of the summary effects (data available upon request). We considered applying fixed-effect models; however, the fixed-effect model does not account for variation in intervention effects across studies. Therefore, we used random-effects models for all four outcomes and made assumptions about the extent of heterogeneity. We used the information provided by Rhodes et al. to construct informative priors for the between-study variance ( $\tau^2$ ).<sup>112</sup> ([see Table D2.1](#)) All NMAs were conducted using the IndiRect NMA platform (CRG-EVERSANA, 2020™). We initially discarded the first 10,000 iterations as “burn-in” and based inferences on an additional 50,000 iterations using three chains. We evaluated the convergence of chains through visual examination of the Brook–Gelman–Rubin diagnostic and historical plots.

**Figure D2.1. Network Diagram**



**Table D2.1. NMAs Conducted & Presented**

| Outcome                                  | Model   | Number of trials |
|--|---|------------------|
| Change from Baseline in HbA1c (%)        | Generalized linear model with identity link;<br>Random effect model with informative prior (prior for between study variance: $\log t[-3.68, 2.78^2, 5]$ ) <sup>112</sup> | 5                |
| Change from Baseline in Body Weight (kg) | Generalized linear model with identity link;<br>Random effect with informative prior (prior for between study variance: $\log t[-3.44, 2.44^2, 5]$ ) <sup>112</sup>       |                  |
| Change from Baseline in LDL (mg/dL)      | Generalized linear model with identity link;<br>Random effect model with informative prior (prior for between study variance: $\log t[-3.68, 2.78^2, 5]$ ) <sup>112</sup> |                  |
| Change from Baseline in SBP (mmHg)       | Generalized linear model with identity link;<br>Random effect with informative prior (prior for between study variance: $\log t[-3.44, 2.44^2, 5]$ ) <sup>112</sup>       |                  |

%, percentage point, HbA1c: hemoglobin A1c, kg: kilogram, LDL: low-density lipoprotein, mg/dL: milligram/deciliter, mmHg: millimeters of mercury, SBP: systolic blood pressure

**Table D2.2. Data Inputs for NMA of HbA1c and Body Weight Loss**

|            |      | HbA1C (%) |       |                | Body Weight (kg) |       |                |
|------------|------|-----------|-------|----------------|------------------|-------|----------------|
| Trial      | Name | N         | Mean  | Standard Error | N                | Mean  | Standard Error |
| SURPASS-2  | TZP  |           | -2.3  |                |                  | -11.2 |                |
|            | SEM  |           | -1.86 |                |                  | -5.7  |                |
| SUSTAIN 2  | SEM  |           |       |                |                  |       |                |
|            | SITA |           |       |                |                  |       |                |
| PIONEER 2  | OSEM |           |       |                |                  |       |                |
|            | EMPA |           |       |                |                  |       |                |
| PIONEER 3  | OSEM |           |       |                |                  |       |                |
|            | SITA |           |       |                |                  |       |                |
| HARMONY 3* | PBO  | 101       | 0     | 0.13           | 101              | -0.7  | 1.9            |
|            | SITA | 302       | -0.5  | 0.07           | 302              | -0.5  | 1.0            |

%; percentage point, HbA1c: hemoglobin A1c, EMPA: empagliflozin, kg: kilogram, N: number, OSEM: oral semaglutide, PBO: placebo, SEM: semaglutide, SITA: sitagliptin, TZP: tirzepatide

\*Values from HARMONY 3 were digitized by ICER staff

**Table D2.3. Data Inputs for NMA of LDL and SBP**

|            |      | LDL Cholesterol (mg/dL) |      |                | Systolic Blood Pressure (mmHg) |      |                |
|------------|------|-------------------------|------|----------------|--------------------------------|------|----------------|
| Trial      | Name | N                       | Mean | Standard Error | N                              | Mean | Standard Error |
| SURPASS-2  | TZP  |                         | -4.5 |                |                                | -6.5 |                |
|            | SEM  |                         | -5.6 |                |                                | -3.6 |                |
| SUSTAIN 2  | SEM  |                         |      |                |                                |      |                |
|            | SITA |                         |      |                |                                |      |                |
| PIONEER 2  | OSEM |                         |      |                |                                |      |                |
|            | EMPA |                         |      |                |                                |      |                |
| PIONEER 3  | OSEM |                         |      |                |                                |      |                |
|            | SITA |                         |      |                |                                |      |                |
| HARMONY 3* | PBO  | 101                     | -1.2 | 2.7            | 101                            | 2.2  | 1.39           |
|            | SITA | 302                     | -1.9 | 1.34           | 302                            | 0.2  | 0.85           |

EMPA: empagliflozin, LDL: low-density lipoprotein, mg/dL: milligrams per deciliter, N: number, OSEM: oral semaglutide, PBO: placebo, SBP: systolic blood pressure, SEM: semaglutide, SITA: sitagliptin, TZP: tirzepatide

\*Note: For LDL and SBP, mean values of change were calculated from baseline to week 104.

**Table D2.4. NMA Results for Change in HbA1c, Body Weight, LDL and SBP at Week 40 Between Tirzepatide vs. Background Therapy/Empagliflozin**

|                           | TZP vs. BT                              | TZP vs. EMPA           |
|---------------------------|---|------------------------|
|                           | Mean Difference (95% Credible Interval) |                        |
| Change in HbA1c, %        | -1.72 (-1.95 to -1.49)                  | -1.12 (-1.39 to -0.85) |
| Change in Body Weight, kg | -9.51 (-10.3 to -8.73)                  | -7.24 (-8.08 to -6.41) |
| Change in LDL, mg/dL      | -4.34 (-5.42 to -3.26)                  | -7.53 (-8.67 to -6.38) |
| Change in SBP, mmHg       | -7.46 (-8.11 to -6.82)                  | -2.59 (-3.29 to -1.90) |

%; percentage point, BT: background therapy, EMPA: empagliflozin, HbA1c: hemoglobin A1c, kg: kilogram, LDL: low-density lipoprotein, mg/dL: milligram per deciliter, mmHg: millimeters of mercury, SBP: systolic blood pressure, TZP: tirzepatide

## D3. Additional Clinical Evidence

### Trials of Tirzepatide

We identified four relevant trials of tirzepatide for treatment of T2DM.<sup>5,6,32,34</sup> The key trials are described in detail below and additional details can be found in Evidence Table D4.3.-6. Frias 2018, Frias 2020, and SURPASS-2 have been published and the data for these trials are informed by the clinical trial report. We also identified SURPASS-4 which includes an assessment of the cardiovascular safety of tirzepatide compared with insulin glargine.

#### Phase 2 (Frias 2018 and 2020)

Frias 2018 and 2020 are two Phase 2 trials exploring the efficacy and safety of tirzepatide in patients with T2DM. Frias 2018 was a 26-week randomized, double-blind study where participants were randomized 1:1:1:1 to 1 mg (n=52), 5 mg (n=55), 10 mg (n=51), 15 mg (n=53) of tirzepatide, 1.5 mg of dulaglutide (n=52), or placebo (n=51). For the purposes of this review, only the 5, 10, and 15 mg tirzepatide arms were included as Eli Lilly is not seeking FDA approval for the 1 mg dose. Patients were eligible for the study if they were 18-75 years old with T2DM for at least six months, that was inadequately controlled with diet and exercise alone or with stable metformin therapy for at least 3 months before screening, and a BMI of 23-50 kg/m<sup>2</sup>. The primary outcome was change in HbA1c from baseline at 26 weeks. Secondary outcomes include change in HbA1c at week 12, change in mean bodyweight, and waist circumference from baseline to weeks 12 and 26.

Frias 2020 was a Phase 2 dose-ranging study, where patients were randomized to either placebo or one of three tirzepatide doses. For the purpose of this review, the 12 mg arm was not reported on, as Eli Lilly will not be seeking FDA approval for this dose. The two 15 mg arms had different dose titration regimens; the 15 mg-1 group was 2.5 mg for two weeks followed by 5 mg for 2 weeks, 10 mg for 4 weeks and then 15 mg for the final 4 weeks. The 15 mg-2 arm was 2.5 mg for 4 weeks,

followed by 7.5 mg for 4 weeks, and then 15 mg for the final 4 weeks. Inclusion criteria and outcomes were similar to the 2018 study. The timepoint of interest was 12 weeks.

Additional baseline characteristics are available in [Evidence Table D4.3](#).

### SURPASS-2

SURPASS-2 was a Phase 3, head-to-head open-label trial exploring the efficacy and safety of tirzepatide compared to injectable semaglutide. Patients were randomized 1:1:1:1 to tirzepatide 5 mg (n= 470), 10 mg (n= 469), 15 mg (n= 470) or semaglutide 1 mg (n= 469) every week for 40 weeks followed by a 4-week safety period. 1,878 patients included in the study were adults with T2DM that were inadequately controlled with at least 1500 mg of metformin per day. Included patients also had HbA1c levels of 7.0 to 10.5% and a BMI of  $\geq 25$  kg/m<sup>2</sup> with a stable weight in the past three months. Patients with type 1 diabetes, an eGFR below 45 mL/min/1.73 m<sup>2</sup>, and a history of pancreatitis were excluded from the study. Included patients had a mean age of 56.6 years, with 53% identifying as female, 82.6% white, an average weight of 93.7 kg, and an eGFR of 96.0 mL/min/1.73 m<sup>2</sup>. Additional baseline characteristics are available in Evidence Table D4.3.

The primary endpoint was change in HbA1c from baseline to week 40. Secondary endpoints include change from body weight, and attainment of HbA1c targets of less than 7.0% and less than 5.7%.

### SURPASS-4

SURPASS-4 was an open-label Phase 3 study exploring the efficacy and cardiovascular safety of tirzepatide (5, 10 and 15 mg) versus insulin glargine in patients with T2DM. Patients were randomized to either a tirzepatide arm (n=995) or insulin glargine (n=1000) for 52-weeks for the primary efficacy endpoint, with an additional variable treatment period of up to 52 additional weeks. The median study duration was 85 weeks. Study participants were adults with T2DM inadequately controlled with any of three oral glucose-lowering medications (i.e., metformin, sulfonylurea, or an SGLT-2 inhibitor), a BMI of 25 kg/m<sup>2</sup> or more and stable weight and increased risk of CV events. Patients with type 1 diabetes or a history of pancreatitis were not included in the study. Included patients had a mean disease duration of 10.5 years, baseline HbA1c of 8.52%, and a baseline weight of 90.3 kg. 87% of patients had a history of cardiovascular disease.

The primary endpoint was change in HbA1c from baseline to 52 weeks. Key secondary endpoints include change in bodyweight at 52 and achievement of HbA1c target of less than 7%. A prespecified cardiovascular risk comparison between tirzepatide and insulin glargine was also conducted and assessed MACE-4. Additional outcomes are available in [Evidence Table D4.12](#).



## **Trials of NMA Linkage Studies**

We identified four trials to provide linkages for the NMA.<sup>38,113-115</sup> The trials are described below and additional details can be found in [Evidence Tables D4.7-9](#). All trials are published and are informed by the respective clinical trial reports.

### **SUSTAIN-2**

SUSTAIN-2 was a Phase 3a, randomized, double blind, multicenter trial, assessing the efficacy and safety of semaglutide versus sitagliptin in patients with T2DM inadequately controlled on metformin, thiazolidinediones, or both. Included patients were adults with T2DM with insufficient glycemic control for 90 days prior to screening and were on stable treatment with metformin, pioglitazone, rosiglitazone, or metformin and rosiglitazone. Patients were excluded if they were on other glucose lowering drugs not described above, had a history of chronic or acute pancreatitis, impaired renal function, or heart failure at any time. 1,231 patients were randomized 2:2:1:1 to 0.5 mg semaglutide (n=409), 1.0 mg semaglutide (n=409) or two arms of 100 mg sitagliptin that were pooled for analysis (n=407). Included patients had a mean age of 55.1, years, HbA1c of 64.7 mmol/mol, 49.5% female, 68.5% white and an eGFR of 97.50 mL/min/1.73 m<sup>2</sup>. Additional baseline characteristics are available in [Evidence Table D4.7](#).

The primary outcome was change in HbA1c from baseline at week 56. Secondary endpoints include change in bodyweight, proportion of patients who achieved an HbA1c of less than 7.0% and HbA1c of 6.5%.

### **PIONEER 2 and PIONEER 3**

PIONEER 2 and 3 have been previously described in the 2019 T2DM ICER report.<sup>39</sup> A brief description is provided below.

The PIONEER program was comprised of 10 trials (PIONEER 1-10). The PIONEER trials included in this review (PIONEER 2 and 3) were multinational RCTs comparing oral semaglutide to sitagliptin, empagliflozin, liraglutide, and placebo. PIONEER 2 compared oral semaglutide 14 mg to empagliflozin 25 mg added to metformin and PIONEER 3 compared oral semaglutide 3, 7, and 14 mg to sitagliptin 100 mg added to metformin ± sulfonylurea (47%). Key exclusion criteria included: renal impairment (eGFR <60 mL/min/1.73 m<sup>2</sup>); MI, stroke, hospitalization for unstable angina, or transient ischemic attack within 180 days; stage IV heart failure; and history of pancreatitis. Baseline characteristics are available in [Evidence Table D4.7](#).

### **HARMONY-3**

The HARMONY 3 trial was a Phase 3 randomized, double-blind, placebo-controlled study and evaluated the efficacy and safety of albiglutide versus daily sitagliptin, daily glimepiride, and

placebo in patients with type 2 diabetes. For the purpose of this review, we only used the placebo and sitagliptin arms for the NMA. Patients were eligible to be enrolled if they were adults with T2DM and experienced inadequate glycemic control while taking background metformin at least 3 months before screening. Patients also had to have a HbA1c of 7.0% to 10% and a BMI of 20 to 45 kg/m<sup>2</sup>. 1049 patients met the criteria (placebo, n=101 and sitagliptin, n=302) with a mean age of 54.3 to 56.1, and a mean duration of diabetes from 5.8 to 6.7 years. Additional baseline characteristics are available in [Evidence Table D4.7](#).

The primary outcome was change in HbA1c from baseline to week 104. The secondary endpoints include change from baseline for HbA1c and weight.

## **Cardiovascular Outcomes Trials (CVOT)**

We identified two relevant trials exploring the efficacy of semaglutide and empagliflozin on cardiovascular outcomes.<sup>7,8</sup> The trials are described below with additional details on study design available in [Evidence Table D4.2](#).

### **SUSTAIN-6**

The SUSTAIN-6 trial was a Phase 3 randomized, double-blind, placebo-controlled trial evaluating the cardiovascular safety of semaglutide in patients with T2DM. Patients were randomized 1:1:1:1 to either 0.5 or 1.0 mg injectable semaglutide or a matched placebo for 104 weeks with a 5-week follow up period. 3,297 adults met the inclusion criteria of T2DM and HbA1c levels of 7%, and no previous treatment with an antihyperglycemic drug, or more than two oral antihyperglycemic agents with or without basal or premixed insulin. Patients were also included if they were 50+ years of age with established CVD, chronic heart failure, or chronic kidney disease of stage three or higher. Included patients had a mean age of 64.6 years, an average disease duration of 13.8 years and an average Hba1c level of 8.7%. Additional baseline characteristics are available in [Evidence Table D4.10](#).

The primary composite outcome was first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke (MACE-3). A key secondary outcome was first occurrence of an expanded composite CV outcome (death from CV causes, nonfatal MI, nonfatal stroke, revascularization and hospitalization for unstable angina or heart failure).

### **EMPA-REG -OUTCOME**

The EMPA-REG OUTCOME trial was a Phase 3 trial evaluating the efficacy and safety of empagliflozin added to standard of care on cardiovascular morbidity and mortality in patients with T2DM and high cardiovascular risk. Patients were eligible for the trial if they were 18 or older with T2DM, a BMI of 45 kg/m<sup>2</sup> or less and eGFR of at least 30 mL/min/1.73m<sup>2</sup> and established CVD. Included patients were randomized 1:1:1 to either two doses of EMPA (N=4687) or placebo

(N=2133). The baseline characteristics were well balanced, with a mean age of 63.1, mean weight of 86.3 kg and a HbA1c of 8.07%. Median observation time was 3.1 years. Additional baseline characteristics are available in [Evidence table D4.10](#).

The primary outcome was MACE-3. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina.

## D4. Evidence Tables

**Table D4.1. USPSTF Study Quality**

| Trial                   | Comparable Groups | Non-differential Follow-up | Patient/ Investigator Blinding | Clear Definition of Intervention | Clear Definitions of Outcomes | Selective Outcome Reporting | Measurements Valid | Intention-to-treat Analysis | Approach to Missing Data | USPSTF Rating |
|-------------------------|-------------------|----------------------------|--------------------------------|----------------------------------|-------------------------------|-----------------------------|--------------------|-----------------------------|--------------------------|---------------|
| Tirzepatide             |                   |                            |                                |                                  |                               |                             |                    |                             |                          |               |
| <b>Frias 2018</b>       | Yes               | Yes                        | Yes                            | Yes                              | Yes                           | No                          | Yes                | mITT                        | LOCF                     | Good          |
| <b>Frias 2020</b>       | Yes               | No                         | Yes                            | Yes                              | Yes                           | No                          | Yes                | mITT                        | MMRM                     | Fair          |
| <b>SURPASS-2</b>        | Yes               | Yes                        | Open-label                     | Yes                              | Yes                           | No                          | Yes                | mITT                        | MMRM                     | Good          |
| <b>SURPASS-4</b>        | Yes               | Yes                        | Open-label                     | Yes                              | Yes                           | No                          | Yes                | mITT                        | MMRM                     | Good          |
| Injectable Semaglutide  |                   |                            |                                |                                  |                               |                             |                    |                             |                          |               |
| <b>SUSTAIN-2</b>        | Yes               | Yes                        | Yes                            | Yes                              | Yes                           | No                          | Yes                | mITT                        | MI                       | Good          |
| <b>SUSTAIN-6</b>        | Yes               | Yes                        | Yes                            | Yes                              | Yes                           | No                          | Yes                | ITT                         | MAR                      | Good          |
| Oral Semaglutide*       |                   |                            |                                |                                  |                               |                             |                    |                             |                          |               |
| <b>PIONEER 2</b>        | Yes               | Yes                        | Open-label                     | Yes                              | Yes                           | No                          | Yes                | ITT                         | MI                       | Good          |
| <b>PIONEER 3</b>        | Yes               | Yes                        | Yes                            | Yes                              | Yes                           | No                          | Yes                | ITT                         | MI                       | Good          |
| Empagliflozin           |                   |                            |                                |                                  |                               |                             |                    |                             |                          |               |
| <b>EMPA-REG OUTCOME</b> | Yes               | Yes                        | Yes                            | Yes                              | Yes                           | No                          | Yes                | mITT                        | LOCF                     | Good          |
| Sitagliptin*            |                   |                            |                                |                                  |                               |                             |                    |                             |                          |               |
| <b>HARMONY 3</b>        | Yes               | Yes                        | Yes                            | Yes                              | Yes                           | No                          | Yes                | ITT                         | LOCF                     | Good          |

Studies with an asterisk (\*) were used as linkages for the NMA. ITT: intention-to-treat analysis, LOCF: last observation carried forward, MAR: missing at random, MI: multiple imputation, mITT: modified intention-to-treat analysis, MM: mixed-effects model, MMRM: mixed-effects model repeated measure, NR: not reported, USPSTF: US Preventive Services Task Force

**Table D4.2. Study Design**

| Trial  | Interventions   | Background Therapy | Inclusion Criteria   | Study Length | Primary Key Outcome  | Key Secondary Outcomes   |
|--|---|--------------------|--|--------------|--|--|
| <b>Tirzepatide</b>   |   |                    |  |              |  |  |
| <b>Phase 2</b><br><b>Frias 2018</b><br><br><b>N=318</b><br><br><b>18 to 75 years</b> | PBO<br>TZP 1 mg<br>TZP 5 mg<br>TZP 10 mg<br>TZP 15 mg<br>DUA 1.5 mg | +/- MET            | Have had T2DM for $\geq 6$ months according to WHO classification<br><br>Have HbA1c of 7.0% to 10.5%<br><br>If on MET, have been treated with stable doses of MET for at least 3 months<br><br>Have BMI $\geq 23$ and $< 50$ kg/m <sup>2</sup> | 26 weeks     | <u>Primary</u><br>Change in HbA1c from baseline to Week 26<br><br>Bayesian Dose Response | <u>Secondary</u><br>Percentage of participants with 5% or greater body weight loss from baseline<br><br>Percentage of participants with 10% or greater body weight loss from baseline<br><br>Percentage of participants reaching the HbA1c target of $\leq 6.5\%$<br><br>Percentage of participants reaching the HbA1c target of $< 7.0\%$ |
| <b>Phase 2</b><br><b>Frias 2020</b><br><br><b>N=111</b><br><br><b>18 to 75 years</b> | TZP 12 mg<br>TZP 15 mg-1<br>TZP 15 mg-2<br>PBO                      | +/- MET            | Have T2DM for $\geq 6$ months according to ADA 2017<br><br>Have HbA1c of 7.0% to 10.5%<br><br>If on MET, have been treated with stable doses of MET for at least 30 months<br><br>Have a BMI between 23 and 45 kg/m <sup>2</sup>               | 12 weeks     | <u>Primary</u><br>Change from baseline in HbA1c  | <u>Secondary</u><br>Change from baseline in body weight<br><br>Change from baseline in waist circumference<br><br>Number of participants with anti-drug antibodies<br><br>Number of episodes of total hypoglycemia episodes<br>Pharmacokinetics (PK):<br>Average trough concentration  |

|  |  |  |  |                 |  |   |
|--|--|--|--|-----------------|--|---|
|  |  |  |  |                 |  | (Conctrough) of tirzepatide   |
| <b>SURPASS-2</b><br><b>Frias 2021</b><br><br><b>N=1,879</b><br><br><b>18 and older</b> | TZP 5 mg<br>TZP 10 mg<br>TZP 15 mg<br>SEM 1 mg                       | MET                                      | Have been diagnosed with T2DM<br><br>Have HbA1c between $\geq 7.0\%$ and $\leq 10.5\%$<br><br>Be on stable treatment with unchanged dose of metformin $>1500$ mg/day for at least 3 months prior to screening<br><br>Be of stable weight ( $\pm 5\%$ ) for at least 3 months before screening  | 40 weeks        | <u>Primary</u><br>Change from Baseline in HbA1c to week 40 | <u>Secondary</u><br>Mean change from baseline in daily average 7-Point SMBG values<br><br>Percentage of participants who achieved weight loss $\geq 5\%$<br><br>Rate of documented symptomatic hypoglycemic episodes<br><br>Change from baseline in body weight<br><br>Percentage of participants achieving an HbA1c target value of $<7\%$ |
| <b>SURPASS-4</b><br><b>Del Proto 2021</b><br><b>N=1878</b><br><br><b>18 and older</b>  | TZP 5 mg<br>TZP 10 mg<br>TZP 15 mg<br>Insulin glargine SC once daily | OADs (MET, SGLT-2 inhibitors, and/or SU) | Have been diagnosed with T2DM<br><br>Have HbA1c between $\geq 7.5\%$ and $\leq 10.5\%$<br><br>Be on stable treatment with unchanged dose of at least 1 and no more than 3 types of OADs, which may only include metformin, SGLT-2 inhibitors, and/or SU for at least 3 months before screening<br><br>Have increased risk for CV events<br><br>Be of stable weight ( $\pm 5\%$ ) | Up to 104 weeks | <u>Primary</u><br>Change from baseline in HbA1c to week 52 | <u>Secondary</u><br>Change from baseline in body weight<br><br>Percentage of participants achieving an HbA1c target value of $<7\%$<br><br>Change from baseline in fasting serum glucose<br>Change from Baseline in HbA1c (5 mg)  |

| Injectable Semaglutide  |  |                                       |  |           |   |   |
|---|--|---------------------------------------|--|-----------|---|---|
| <b>SUSTAIN-2</b><br><b>Ahren 2017</b><br><br><b>N=1231</b><br><br><b>18 and older</b> | SEM 0.5 mg<br>SEM 1.0 mg<br>SITA 100 mg<br>+ PBO 0.5 mg<br>SITA 100 mg<br>+ PBO 1.0 mg | MET ± TZD                             | Japan: Age minimum 20 years<br><br>Subjects diagnosed with T2DM and on stable treatment in a period of 90 days prior to screening with either MET above or equal to 1500 mg (or maximum tolerated dose), pioglitazone above or equal to 30 mg (or maximum tolerated dose), rosiglitazone above or equal to 4 mg (or maximum tolerated dose) or a combination of either MET/pioglitazone or MET/rosiglitazone (doses as for individual therapies) | 56 weeks  | <u>Primary</u><br>Change from Baseline in HbA1c | <u>Secondary</u><br>Change in body weight from baseline<br><br>Change in FPG from baseline<br><br>Change in PRO questionnaire<br><br>Change in systolic and diastolic blood pressure from baseline<br><br>Subjects who achieve HbA1c below or equal to 6.5% (48 mmol/mol) target (yes/no)               |
| <b>SUSTAIN-6</b><br><b>Marso 2016</b><br><br><b>N=3260</b><br><br><b>50 and older</b> | SEM 0.5 mg<br>SEM 1.0 mg<br>PBO 0.5 mg<br>SC QW<br>PBO 1.0 mg<br>SC QW                 | Naïve or treated with OADs or insulin | Men and women with T2DM<br><br>Age above or equal to 50 years at screening and clinical evidence of cardiovascular disease or age above or equal to 60 years at screening and subclinical evidence of cardiovascular disease<br><br>Anti-diabetic drug naïve, or treated with one or two OADs<br><br>HbA1c above or equal to 7.0% at screening   | 148 weeks | <u>Primary</u><br>First occurrence of a MACE    | <u>Secondary</u><br>Change from baseline: urinary albumin to creatinine ratio<br><br>Change from baseline: vital signs<br><br>Time from randomization to first occurrence of an expanded composite cardiovascular outcome<br><br>Change from baseline: HbA1c<br><br>Change from baseline: Lipid profile |

|  |  |            |   |          |  |  |
|--|--|------------|---|----------|--|--|
|  |  |            |   |          |  | Change from baseline FBG   |
| <b>Oral Semaglutide</b>  |  |            |   |          |  |  |
| <b>PIONEER 2</b><br><b>NCT02893328</b><br><b>Rodbard et al.</b><br><br><b>N=822</b><br><br><b>18 and older</b>   | SEM 14 mg<br>EMPA 25 mg                          | MET        | Male or female, age above or equal to 18 years at the time of signing informed consent<br><br>Diagnosed with T2DM at least 90 days prior to day of screening<br><br>HbA1c of 7.0 to 10.5% (53-91 mmol/mol)<br><br>Stable daily dose of metformin (at least 1500 mg or MTD) at least 90 days prior to the day of screening | 52 weeks | <u>Primary</u><br>Change in HbA1c (week 0 to 26) | <u>Secondary</u><br>Change in body weight (kg) (week 0 to 26)<br><br>Change in HbA1c (week 0 to 52)<br><br>Change in body weight (kg) (week 0 to 52)<br><br>Change in FPG  |
| <b>PIONEER 3</b><br><b>NCT026865</b><br><b>Rosenstock et al.</b><br><br><b>N=1864</b><br><br><b>18 and older</b> | SEM 3 mg<br>SEM 7 mg<br>SEM 14 mg<br>SITA 100 mg | MET +/- SU | Male or female, age at least 18 years at the time of signing informed consent<br><br>Diagnosed with T2DM for at least 90 days prior to day of screening<br><br>HbA1c 7.0-10.5% (53-91 mmol/mol)<br><br>Stable daily dose of MET (at least 1500 mg or MTD) within 90 days prior to the day of screening                    | 78 weeks | <u>Primary</u><br>Change in HbA1c (week 0 to 26) | <u>Secondary</u><br>Change in body weight (week 0 to 26)<br><br>Change in HbA1c (weeks 0 to 52, 78)<br><br>Change in body weight (kg) (weeks 0 to 52,78)<br><br>Change in body weight (%)<br><br>Change in FPG<br><br>Change in BMI<br><br>Change in waist circumference |
| <b>Empagliflozin</b>   |  |            |   |          |  |  |



|  |                                 |  |   |                 |  |   |
|--|---------------------------------|--|---|-----------------|--|---|
| <b>EMPA- REG OUTCOME (CVOT)</b><br><b>NCT01131676</b><br><b>Zinman et al.</b><br><br><b>N=7064</b> | EMPA 10 mg<br>EMPA 25 mg<br>PBO | Naïve or pre-treated with any background therapy | Diagnosis of T2DM<br><br>Male or female patients on diet and exercise regimen who are drug naïve or pre-treated with any background therapy<br><br>Antidiabetic therapy has to be unchanged for 12 weeks prior to randomization<br><br>HbA1c of $\geq 7.0\%$ and $\leq 10\%$ for patients on background therapy or HbA1c $\geq 7.0\%$ and $\leq 9.0\%$ for drug naïve patients<br><br>Age $\geq 18$ years<br><br>BMI $\leq 45$ kg/m <sup>2</sup> at Visit 1 | Up to 4.6 years | <u>Primary</u><br>Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint (MACE-3):<br>CV<br>Death (including fatal stroke and fatal MI)<br>Non-fatal MI (excluding silent MI)<br>Non-fatal Stroke | <u>Secondary</u><br>Percentage of participants with the composite of all events adjudicated (MACE-4):<br>CV<br>Death (including fatal stroke and fatal MI)<br>Non-fatal MI (excluding silent MI)<br>Non-fatal stroke<br>Hospitalization for Unstable Angina Pectoris<br>Percentage of participants with silent MI |
|--|---------------------------------|--|---|-----------------|--|---|

BMI: body mass index, CVOT: cardiovascular outcomes trial, DUA: dulaglutide, EMPA: empagliflozin, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, MACE: major adverse cardiovascular event, MACE-3: 3-point MACE, MACE-4: 4-point MACE, MET: metformin, mg: milligram, MTD: maximum tolerated dose, OAD: oral antidiabetic drug, PBO: placebo, PK: pharmacokinetics, PRO: patient-reported outcomes, QW: once weekly, SC: subcutaneous, SEM: semaglutide, SGLT-2: sodium-dependent glucose co-transporter-2, SIT: sitagliptin, SMBG: self-monitoring of blood glucose, SU: sulfonylurea, TZP: tirzepatide, T2DM: type 2 diabetes mellitus

**Table D4.3. Baseline Characteristics – Tirzepatide<sup>5,6,32,34</sup>**

| Study                   |                  | Frias 2018      |                |                 |                 | Frias 2020       |                  |                  | SURPASS -2        |                   |                   |                   | SURPASS-4       |                 |                     |                     |                     |
|-------------------------|------------------|-----------------|----------------|-----------------|-----------------|------------------|------------------|------------------|-------------------|-------------------|-------------------|-------------------|-----------------|-----------------|---------------------|---------------------|---------------------|
| Arm                     |                  | PBO             | TZP<br>5 mg    | TZP<br>10 mg    | TZP<br>15 mg    | PBO              | TZP 15<br>mg-1   | TZP 15<br>mg-2   | TZP<br>5 mg       | TZP 10<br>mg      | TZP 15<br>mg      | SEM<br>1 mg       | TZP 5<br>mg     | TZP 10<br>mg    | TZP<br>15mg         | Insulin<br>G        | Overall<br>I        |
| N                       |                  | 51              | 55             | 51              | 53              | 26               | 28               | 28               | 470               | 469               | 470               | 469               | 329             | 328             | 338                 | 1000                | 1995                |
| Age, y                  | Mean (SD)        | 56.6<br>(8.9)   | 57.9<br>(8.2)  | 56.5<br>(9.9)   | 56.0<br>(7.6)   | 56.0<br>(10.13)  | 55.5<br>(8.54)   | 56.6<br>(9.21)   | 56.3<br>(10.0)    | 57.2<br>(10.5)    | 55.9<br>(10.4)    | 56.9<br>(52)      | 62.9<br>(8.6)   | 63.7<br>(8.7)   | 63.7<br>(8.6)       | 63.8<br>(8.5)       | 63.6<br>(8.6)       |
| Sex, n (%)              | Men              | 29 (57)         | 34<br>(62)     | 30<br>(59)      | 22<br>(42)      | 12<br>(46.2)     | 16<br>(57.1)     | 23<br>(82.1)     | 205<br>(43.6)     | 238<br>(50.7)     | 214<br>(45.5)     | 225<br>(48)       | 198<br>(60)     | 209<br>(64)     | 203<br>(60)         | 636<br>(64)         | 1246<br>(62)        |
|                         | Women            | 22 (43)         | 21<br>(38)     | 21<br>(41)      | 31<br>(59)      | NR               | NR               | NR               | 265<br>(56.4)     | 231<br>(49.2)     | 256<br>(54.5)     | 244<br>(52.0)     | 131<br>(40)     | 119<br>(36)     | 135<br>(40)         | 364<br>(36)         | 749<br>(38)         |
| Diabetes<br>Duration, y | Mean             | 8.6             | 8.9            | 7.9             | 8.5             | 8.8              | 8.2              | 8.9              | 9.1               | 8.4               | 8.7               | 8.3               | 9.8             | 10.6            | 10.4                | 10.7                | 10.5                |
|                         | SD               | 7               | 5.7            | 5.8             | 6.1             | 6.43             | 4.87             | 6.35             | 7.16              | 5.9               | 6.85              | 5.8               | 6.2-<br>15.3    | 6.5-<br>16.2    | 5.5-<br>15.7        | 6.3-<br>16.5        | 6.2-<br>15.9        |
| HbA1c<br>mean (SD)      | %                | 8.0<br>(0.9)    | 8.2<br>(1.0)   | 8.2<br>(1.1)    | 8.1<br>(1.1)    | 8.2<br>(1.2)     | 8.5<br>(1.2)     | 8.4<br>(1.1)     | 8.3<br>(1.1)      | 8.3<br>(1.0)      | 8.3<br>(1.0)      | 8.3<br>(1.0)      | 8.52<br>(0.84)  | 8.59<br>(0.91)  | 8.52<br>(0.98)      | 8.50<br>(0.85)      | 8.52<br>(0.88)      |
| Weight, kg              | Mean             | 91.5            | 92.8           | 92.7            | 89.1            | 89.6             | 88.7             | 89.6             | 92.5              | 94.8              | 93.8              | 93.7              | 90.3            | 90.6            | 90                  | 90.2                | 90.3                |
|                         | SD               | 23.1            | 19             | 19.5            | 22.7            | 23.7             | 18.21            | 16.91            | 21.76             | 22.71             | 21.83             | 21.12             | 20.32           | 18.21           | 16.34               | 19                  | 18.66               |
| BMI, kg/m <sup>2</sup>  | Mean<br>(SD)     | 32.4<br>(6.0)   | 32.9<br>(5.7)  | 32.6<br>(5.8)   | 32.2<br>(6.2)   | 32.5<br>(5.7)    | 32.0<br>(5.56)   | 31.1<br>(4.21)   | 33.8<br>(6.85)    | 34.3<br>(6.60)    | 34.5<br>(7.11)    | 34.2<br>(7.15)    | 32.6<br>(6.06)  | 32.8<br>(5.51)  | 32.5<br>(5.02)      | 34.5<br>(5.55)      | 32.6<br>(5.54)      |
| Waist, cm               | Mean (SD)        | 107.7<br>(2.06) | 110.1<br>(2.0) | 109.6<br>(2.04) | 107.6<br>(2.17) | 109.1<br>(15.38) | 107.0<br>(12.65) | 105.1<br>(12.19) | 108.06<br>(14.81) | 110.55<br>(16.05) | 109.55<br>(15.60) | 109.04<br>(14.90) | NR              | NR              | NR                  | NR                  | NR                  |
| eGFR                    | Mean (SD)        | 95.3<br>(15.3)  | 92.2<br>(17.2) | 93.7<br>(18.6)  | 91.8<br>(17.9)  | NR               | NR               | NR               | 96.6<br>(17.51)   | 95.5<br>(16.62)   | 96.3<br>(16.92)   | 95.6<br>(17.25)   | 80.3<br>(22.66) | 81.4<br>(20.44) | 81.6<br>(21.22<br>) | 81.5<br>(20.78<br>) | 81.3<br>(21.11<br>) |
| Metformin<br>use, N (%) | Yes              | 47<br>(92.2)    | 49<br>(89.1)   | 44<br>(86.3)    | 51<br>(96.2)    | 23<br>(88.5)     | 25<br>(89.3)     | 23<br>(82.1)     | 470<br>(100)      | 469<br>(100)      | 470<br>(100)      | 469<br>(100)      | 306<br>(93)     | 316<br>(96)     | 317<br>(94)         | 954<br>(95)         | 1893<br>(95)        |
| Ethnicity, N<br>(%)     | Hispanic         | 27 (59)         | 22<br>(49)     | 26<br>(57)      | 23<br>(46)      | NR               | NR               | NR               | 325<br>(69.1)     | 322<br>(68.7)     | 334<br>(71.1)     | 336<br>(71.6)     | NR              | NR              | NR                  | NR                  | NR                  |
|                         | Non-<br>Hispanic | 19 (41)         | 23<br>(51)     | 20<br>(44)      | 27<br>(54)      | NR               | NR               | NR               | 145<br>(30.9)     | 147<br>(31.3)     | 136<br>(28.9)     | 133<br>(28.4)     | NR              | NR              | NR                  | NR                  | NR                  |

|                    |                               |         |         |         |         |    |    |    |            |            |            |            |          |          |          |          |           |
|--------------------|-------------------------------|---------|---------|---------|---------|----|----|----|------------|------------|------------|------------|----------|----------|----------|----------|-----------|
| <b>Race, N (%)</b> | American Indian/Alaska Native | NR      | NR      | NR      | NR      | NR | NR | NR | 53 (11.3)  | 53 (11.3)  | 57 (12.1)  | 45 (9.6)   | NR       | NR       | NR       | NR       | NR        |
|                    | Black                         | 2 (4)   | 6 (11)  | 7 (14)  | 6 (11)  | NR | NR | NR | 28 (6.0)   | 21 (4.5)   | 15 (3.2)   | 15 (3.2)   | 13 (4)   | 17 (5)   | 11 (3)   | 32 (3)   | 73 (4)    |
|                    | Asian                         | 1 (2)   | 0       | 1 (2)   | 1 (2)   | NR | NR | NR | 6 (1.3)    | 11 (2.3)   | 5 (1.1)    | 3 (0.6)    | 15 (5)   | 16 (5)   | 8 (2)    | 31 (3)   | 70 (4)    |
|                    | White                         | 41 (80) | 46 (84) | 37 (74) | 43 (81) | NR | NR | NR | 382 (81.3) | 376 (80.2) | 334 (71.1) | 336 (71.6) | 260 (79) | 259 (79) | 285 (85) | 825 (83) | 1629 (82) |

A dulaglutide arm and 1mg tirzepatide arm in Frias 2018 and 12mg Tirzepatide arm in Frias 2020 are also available. Frias 2020 has two 15-mg arms following two different dosing schedules. N: number, NR: not reported, PBO: placebo, SD: standard deviation, TZP: tirzepatide

**Table D4.4. Outcomes– Tirzepatide Phase 2 Trials** <sup>5,32</sup>

| Study                         |                      | Frias 2018 |                |                |                | Frias 2020 |              |              |              |
|-------------------------------|----------------------|------------|----------------|----------------|----------------|------------|--------------|--------------|--------------|
| Arm                           |                      | PBO        | TZP 5 mg       | TZP 10 mg      | TZP 15 mg      | PBO        | TZP 12 mg    | TZP 15 mg-1  | TZP 15 mg-2  |
| N                             |                      | 51         | 55             | 51             | 53             | 26         | 29           | 28           | 28           |
| Timepoint                     |                      | 26 wks     |                |                |                | 12 wks     |              |              |              |
| Glycemia Endpoints            |                      |            |                |                |                |            |              |              |              |
| HbA1c, %                      | Mean, Change from BL | 0.1        | -1.6           | -2             | -2.4           | 0.2        | -1.7         | -2           | -1.8         |
|                               | ETD                  | NR         | NR             | NR             | NR             | REF        | -1.9         | -2.2         | -2           |
|                               | 95% CI (ETD)         | REF        | -1.88 to -1.46 | -2.04 to -1.61 | -2.11 to -1.67 | REF        | -2.5 to -1.4 | -2.8 to -1.7 | -2.5 to -1.4 |
|                               | p-value (ETD)        | REF        | <0.0001        | <0.0001        | <0.0001        | REF        | <0.001       | <0.001       | <0.001       |
| Lipid Levels                  |                      |            |                |                |                |            |              |              |              |
| Triglycerides, mg/dL          | Change from BL       | 26.6       | -44.3          | -62            | -70.9          | NR         | NR           | NR           | NR           |
| Total Cholesterol, mg/dL      | Change from BL       | 11.6       | -3.9           | -11.6          | -11.6          | NR         | NR           | NR           | NR           |
| HDL Cholesterol, mg/dL        | Change from BL       | 0          | 0              | 0              | 3.9            | NR         | NR           | NR           | NR           |
| LDL Cholesterol, mg/dL        | Change from BL       | 7.7        | 0              | 0              | -3.9           | NR         | NR           | NR           | NR           |
| Body Weight Endpoints         |                      |            |                |                |                |            |              |              |              |
| Weight, kg                    | Change from BL       | -0.4       | -4.8           | -8.7           | -11.3          | -0.5       | -5.3         | -5.5         | -5.7         |
|                               | ETD                  | NR         | NR             | NR             | NR             | REF        | -4.8         | -5           | -5.2         |
|                               | 95% CI               | NR         | NR             | NR             | NR             | REF        | -7.1 to -2.6 | -7.2 to -2.7 | -7.5 to -2.9 |
|                               | p-value              | NR         | NR             | NR             | NR             | REF        | <0.001       | <0.001       | <0.001       |
| Mean Waist Circumference      | Change from BL, cm   | -1.3       | -5.1           | -7.4           | -10.2          | -2.5       | -4.8         | -4.9         | -4.9         |
|                               | ETD                  | NR         | NR             | NR             | NR             | REF        | -2.2         | -2.4         | -2.4         |
|                               | 95% CI               | NR         | NR             | NR             | NR             | REF        | -4.7 to 0.2  | -4.9 to 0.1  | -4.9 to -0.2 |
|                               | p-value              | NR         | NR             | NR             | NR             | REF        | 0.075        | 0.065        | 0.065        |
| Blood Pressure and Pulse Rate |                      |            |                |                |                |            |              |              |              |
| DBP, mmHg                     | Change from BL       | 0.8 (1.26) | -0.7 (1.18)    | -0.2 (1.22)    | -0.7 (1.27)    | NR         | NR           | NR           | NR           |

|                                     |                |            |                         |                         |                         |    |    |    |    |
|-------------------------------------|----------------|------------|-------------------------|-------------------------|-------------------------|----|----|----|----|
|                                     | ETD            | NR         | NR                      | NR                      | NR                      | NR | NR | NR | NR |
|                                     | 95% CI         | NR         | NR                      | NR                      | NR                      | NR | NR | NR | NR |
|                                     | p-value        | NR         | NR                      | NR                      | NR                      | NR | NR | NR | NR |
| <b>SBP, mmHg</b>                    | Change from BL | 1.7 (1.98) | -2.6 (1.86)             | -1.3 (1.92)             | -1.0 (2.00)             | NR | NR | NR | NR |
|                                     | ETD            | NR         | NR                      | NR                      | NR                      | NR | NR | NR | NR |
|                                     | 95% CI         | NR         | NR                      | NR                      | NR                      | NR | NR | NR | NR |
|                                     | p-value        | NR         | NR                      | NR                      | NR                      | NR | NR | NR | NR |
| <b>Achieving HbA1C targets</b>      |                |            |                         |                         |                         |    |    |    |    |
| <b>&lt;7%</b>                       | N (%)          | 6 (11.8)   | 38 (69.1)               | 45 (90)                 | 41 (77.4)               | NR | NR | NR | NR |
|                                     | OR (95% CI)    | REF        | 20.98 (7.28 to 60.50)   | 89.44 (24.41 to 327.76) | 33.63 (11.02 to 102.62) | NR | NR | NR | NR |
|                                     | p-value        | REF        | <0.0001                 | <0.0001                 | <0.0001                 | NR | NR | NR | NR |
| <b>&lt;6.5%</b>                     | N (%)          | 1 (2)      | 35 (63.6)               | 41 (82)                 | 31 (58.5)               | NR | NR | NR | NR |
|                                     | OR (95% CI)    | REF        | 73.64 (12.92 to 419.77) | 200.87 (32.74 to >999)  | 56.95 (10.01 to 323.97) | NR | NR | NR | NR |
|                                     | P value        | REF        | <0.0001                 | <0.0001                 | <0.0001                 | NR | NR | NR | NR |
| <b>&lt;5.7%</b>                     | N (%)          | 1 (2)      | 2 (3.6)                 | 9 (18)                  | 16 (30.2)               | NR | NR | NR | NR |
|                                     | OR (95% CI)    | REF        | 1.60 (0.21 to 12.26)    | 7.75 (1.33 to 44.97)    | 14.42 (2.61 to 79.75)   | NR | NR | NR | NR |
|                                     | p-value        | REF        | 0.6506                  | 0.0225                  | 0.0022                  | NR | NR | NR | NR |
| <b>Achieving Bodyweight Targets</b> |                |            |                         |                         |                         |    |    |    |    |
| <b>≥5%</b>                          | N (%)          | 0 (0)      | 26 (47.3)               | 36 (70.6)               | 33 (62.3)               | NR | NR | NR | NR |
|                                     | OR (95% CI)    | REF        | 90.91 (5.45 to >999)    | 236.84 (13.99 to >999)  | 161.12 (9.62 to >999)   | NR | NR | NR | NR |
|                                     | p-value        | REF        | 0.0017                  | 0.0002                  | 0.0004                  | NR | NR | NR | NR |
| <b>≥10 %</b>                        | N (%)          | 0 (0)      | 9 (16.4)                | 20 (39.2)               | 20 (37.7)               | NR | NR | NR | NR |
|                                     | OR (95% CI)    | REF        | 20.82 (1.22 to 355.42)  | 67.57 (4.07 to >999)    | 66.20 (3.99 to >999)    | NR | NR | NR | NR |

|       |             |       |         |           |           |    |    |    |    |
|-------|-------------|-------|---------|-----------|-----------|----|----|----|----|
|       | P value     | REF   | 0.036   | 0.0033    | 0.0034    | NR | NR | NR | NR |
| ≥15 % | N (%)       | 0 (0) | 3 (5.5) | 11 (21.6) | 13 (24.5) | NR | NR | NR | NR |
|       | OR (95% CI) | REF   | NR      | NR        | NR        | NR | NR | NR | NR |
|       | p-value     | REF   | NR      | NR        | NR        | NR | NR | NR | NR |

A dulaglutide arm in Frias 2018 and 12 mg Tirzepatide arm in Frias 2020 are also available. Frias 2020 has two 15-mg arms following two different dosing schedules. BL: baseline, CI: confidence interval, DBP: diastolic blood pressure, ETD: estimated treatment difference, N: number, NR: not reported, OR: odds ratio, PBO: placebo, REF: reference, SBP: systolic blood pressure, SD: standard deviation, TZP: tirzepatide

**Table D4.5. Outcomes– Tirzepatide Phase 3 Trials<sup>6,34</sup>**

| Study                 |                      | SURPASS-2      |                |                |          | SURPASS-4      |                |                |                  |
|-----------------------|----------------------|----------------|----------------|----------------|----------|----------------|----------------|----------------|------------------|
| Arm                   |                      | TZP 5 mg       | TZP 10 mg      | TZP 15 mg      | SEM 1 mg | TZP 5 mg       | TZP 10 mg      | TZP 15 mg      | Insulin Glargine |
| N                     |                      | 470            | 469            | 470            | 469      | 328            | 326            | 337            | 998              |
| Timepoint             |                      | 40 wks         |                |                |          | 52 wks         |                |                |                  |
| Glycemia Endpoints    |                      |                |                |                |          |                |                |                |                  |
| HbA1c, %              | Mean, Change from BL | -2.01          | -2.24          | -2.3           | -1.86    | -2.24          | -2.43          | -2.58          | -1.44            |
|                       | ETD                  | -0.15          | -0.39          | -0.45          | REF      | -0.80          | -0.99          | -1.14          | REF              |
|                       | 95% CI (ETD)         | -0.28 to -0.03 | -0.51 to -0.26 | -0.57 to -0.32 | REF      | -0.92 to -0.68 | -1.11 to -0.87 | -1.26 to -1.02 | REF              |
|                       | p-value (ETD)        | 0.02           | <0.001         | <0.001         | REF      | <0.0001        | <0.0001        | <0.0001        | REF              |
| Lipid levels, mg/dL   |                      |                |                |                |          |                |                |                |                  |
| Triglycerides         | Change from BL       | -31.4*         | -40*           | -41.1*         | -19.1*   | -16.3          | -20.1          | -22.5          | -6.4             |
| Total Cholesterol     | Change from BL       | -9.4*          | -10.2*         | -10.7*         | -8.2*    | -5.2           | -5.5           | -5.6           | 0                |
| HDL Cholesterol       | Change from BL       | 2.9*           | 3.4*           | 3*             | 1.9*     | 6.7            | 9.7            | 10.8           | 2.9              |
| LDL Cholesterol       | Change from BL       | -6.7*          | -4.9*          | -4.5*          | -5.6*    | -6.8           | -8.3           | -7.9           | 1.4              |
| Body Weight Endpoints |                      |                |                |                |          |                |                |                |                  |
| Weight, kg            | Change from BL       | -7.6           | -9.3           | -11.2          | -5.7     | -7.1           | -9.5           | -11.7          | 1.9              |

| Study                         |                | SURPASS-2           |                     |                     |              | SURPASS-4           |                      |                       |                  |
|-------------------------------|----------------|---------------------|---------------------|---------------------|--------------|---------------------|----------------------|-----------------------|------------------|
| Arm                           |                | TZP 5 mg            | TZP 10 mg           | TZP 15 mg           | SEM 1 mg     | TZP 5 mg            | TZP 10 mg            | TZP 15 mg             | Insulin Glargine |
|                               | ETD            | -1.9                | -3.6                | -5.5                | REF          | -9.0                | -11.4                | -13.5                 | REF              |
|                               | 95% CI         | -2.8 to -1.0        | -4.5 to -2.7        | -6.4 to -4.6        | REF          | -9.8 to -8.3        | -12.1 to -10.6       | -12.1 to -10.6        | REF              |
|                               | p-value        | <0.001              | <0.001              | <0.001              | REF          | <0.0001             | <0.0001              | <0.0001               | REF              |
| Mean Waist Circumference, cm  | Change from BL | -6.9*               | -9.6*               | -9.9*               | -5.6*        | -8.41†              | -8.27†               | -9.46†                | 1.4†             |
|                               | ETD            | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
|                               | 95% CI         | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
|                               | p-value        | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
| Blood Pressure and Pulse Rate |                |                     |                     |                     |              |                     |                      |                       |                  |
| DBP, mmHg                     | Change from BL | -4.5                | -5.3                | -6.5                | -3.6         | 1†                  | 0.94†                | 0.8†                  | -0.72†           |
|                               | ETD            | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
|                               | 95% CI         | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
|                               | p-value        | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
| SBP, mmHg                     | Change from BL | NR                  | NR                  | NR                  | NR           | -1.65†              | -4.33†               | -4.59†                | -1.2†            |
|                               | ETD            | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
|                               | 95% CI         | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
|                               | p-value        | NR                  | NR                  | NR                  | NR           | NR                  | NR                   | NR                    | NR               |
| Achieving HbA1c Targets       |                |                     |                     |                     |              |                     |                      |                       |                  |
| <7%                           | N (%)          | 394 (85.5) *        | 408 (88.9) *        | 428 (92.2) *        | 374 (81.1) * | 264 (88)            | 283 (88)             | 303 (91)              | 496 (51)         |
|                               | OR (95% CI)    | 1.54 (1.06 to 2.23) | 2.14 (1.44 to 3.17) | 3.03 (1.97 to 4.66) | REF          | 4.78 (3.47 to 6.58) | 9.23 (6.31 to 13.49) | 11.87 (7.88 to 17.89) | REF              |
|                               | p-value        | NR                  | NR                  | NR                  | NR           | <0.0001             | <0.0001              | <0.0001               | REF              |
| <6.5%                         | N (%)          | 341 (74) *          | 377 (82.1) *        | 404 (87.1) *        | 305 (66.2) * | 215 (66)            | 244 (76)             | 271 (81)              | 310 (32)         |
|                               | OR (95% CI)    | 1.63 (1.2 to 2.21)  | 2.75 (1.98 to 3.82) | 3.95 (2.78 to 5.61) | REF          | 4.86 (3.66 to 6.45) | 8.93 (6.53 to 12.21) | 11.84 (8.52 to 16.45) | REF              |
|                               | p-value        | NR                  | NR                  | NR                  | NR           | <0.0001             | <0.0001              | <0.0001               | REF              |
| <5.7%                         | N (%)          | 135 (29.3) *        | 205 (44.7) *        | 236 (50.9) *        | 91 (19.7) *  | 75 (23)             | 105 (33)             | 144 (43)              | 33 (3)           |

| Study                               |             | SURPASS-2           |                     |                    |              | SURPASS-4              |                        |                         |                  |
|-------------------------------------|-------------|---------------------|---------------------|--------------------|--------------|------------------------|------------------------|-------------------------|------------------|
| Arm                                 |             | TZP 5 mg            | TZP 10 mg           | TZP 15 mg          | SEM 1 mg     | TZP 5 mg               | TZP 10 mg              | TZP 15 mg               | Insulin Glargine |
|                                     | OR (95% CI) | 1.86 (1.35 to 2.57) | 3.94 (2.88 to 5.39) | 5.1 (3.73 to 6.97) | REF          | 9.57 (6.16 to 14.86)   | 17.11 (11.12 to 26.35) | 26.53 (17.35 to 40.56)  | REF              |
|                                     | p-value     | NR                  | NR                  | NR                 | NR           | <0.0001                | <0.0001                | <0.0001                 | REF              |
| <b>Achieving Bodyweight Targets</b> |             |                     |                     |                    |              |                        |                        |                         |                  |
| <b>≥5%</b>                          | N (%)       | 316 (68.6)*         | 378 (82.4) *        | 400 (86.2) *       | 270 (58.4) * | 205 (63)               | 249 (78)               | 285 (85)                | 78 (8)           |
|                                     | OR (95% CI) | 1.58 (1.2 to 2.08)  | 3.49 (2.57, 4.75)   | 4.6 (3.32, 6.38)   | REF          | 21.42 (15.53 to 29.89) | 46.14 (32.05 to 66.42) | 76.93 (51.76 to 114.35) | REF              |
|                                     | p-value     | NR                  | NR                  | NR                 | NR           | <0.0001                | <0.0001                | <0.0001                 | REF              |
| <b>≥10 %</b>                        | N (%)       | 165 (35.8)*         | 243 (52.9)*         | 301 (64.9)*        | 117 (25.3)*  | 117 (36)               | 170 (53)               | 219 (66)                | 15 (2)           |
|                                     | OR (95% CI) | 1.68 (1.26, 2.25)   | 3.58 (2.69, 4.77)   | 5.85 (4.37, 7.82)  | REF          | 20.6 to 61.5)          | 76.79 (44.2 to 132.7)  | 127.5 (73.5 to 221.1)   | REF              |
|                                     | p-value     | NR                  | NR                  | NR                 | NR           | <0.0001                | <0.0001                | <0.0001                 | REF              |
| <b>≥15 %</b>                        | N (%)       | 70 (15.2)*          | 127 (27.7)*         | 185 (39.9)*        | 40 (8.7)*    | 45 (14)                | 77 (24)                | 122 (37)                | 5 (<1)           |
|                                     | OR (95% CI) | 1.92 (1.27, 2.90)   | 4.27 (2.9, 6.29)    | 7.44 (5.09, 10.87) | NR           | 28.58 (11.88 to 68.75) | 59.14 (25 to 139.86)   | 105.74 (45.1 to 247.87) | REF              |
|                                     | p-value     | NR                  | NR                  | NR                 | NR           | <0.0001                | <0.0001                | <0.0001                 | REF              |

Frias 2020 has two 15-mg arms following two different dosing schedules. BL: baseline, CI: confidence interval, DBP: diastolic blood pressure, ETD: estimated treatment difference, N: number, NR: not reported, OR: odds ratio, PBO: placebo, REF: reference, SBP: systolic blood pressure, SD: standard deviation , TZP: tirzepatide OR: odds ratio, CI: confidence interval, BL: baseline, DBP: diastolic blood pressure, SBP: systolic blood pressure

\*Efficacy estimand

†Digitized and calculated by ICER staff



**Table D4.6. Safety – Tirzepatide<sup>5,6,32,34</sup>**

| Study                    | Frias 2018 |           |           |           |            | Frias 2020 |           |             |             | SURPASS-2    |              | SURPASS-4 |           |           |                  |
|--------------------------|------------|-----------|-----------|-----------|------------|------------|-----------|-------------|-------------|--------------|--------------|-----------|-----------|-----------|------------------|
| Arm                      | PBO        | TZP 5 mg  | TZP 10 mg | TZP 15 mg | DUA 1.5 mg | PBO        | TZP 12 mg | TZP 15 mg-1 | TZP 15 mg-2 | TZP 15 mg    | SEM 1 mg     | TZP 5 mg  | TZP 10 mg | TZP 15 mg | Insulin Glargine |
| N                        | 51         | 55        | 51        | 53        | 54         | 26         | 29        | 28          | 28          | 470          | 469          | 328       | 326       | 337       | 998              |
| Timepoint                | 26 wks     |           |           |           |            | 12 wks     |           |             |             | 40 wks       |              | 104 wks   |           |           |                  |
| Any AE                   | NR         | NR        | NR        | NR        | NR         | NR         | NR        | NR          | NR          | 324 (68.9)   | 301 (64.2)   | NR        | NR        | NR        | NR               |
| Any TEAE, n (%)          | 27 (52.9)  | 40 (72.7) | 40 (78.4) | 45 (84.9) | 40 (74.1)  | 13 (50)    | 23 (79.3) | 19 (67.9)   | 24 (85.7)   | NR           | NR           | 232 (71)  | 241 (74)  | 259 (77)  | 679 (68)         |
| D/C Due to AE, n (%)     | 1 (2.0)    | 0         | 1 (2.0)   | 2 (3.8)   | 2 (3.7)    | 0          | 0         | 0           | 0           | 40 (8.5) †** | 19 (4.1) †** | 37 (11)   | 28 (9)    | 36 (11)   | 54 (5)           |
| D/C from Study Drug      | 2 (3.9)    | 5 (9.1)   | 3 (5.9)   | 13 (24.5) | 6 (11.1)   | 1 (3.8)    | 1 (3.4)   | 1 (3.6)     | 0           | NR           | NR           | 8%        | 7%        | 9%        | 3%               |
| Serious AE               | 2 (3.9)    | 1 (1.8)   | 3 (5.9)   | 2 (3.8)   | 3 (5.6)    | 0          | 1 (3.4)   | 0           | 0           | 27 (5.7)     | 13 (2.8)     | 48 (15)   | 54 (17)   | 41 (12)   | 193 (19)         |
| Death                    | 1 (2.0)*   | 0         | 0         | 0         | 0          | 0          | 0         | 0           | 0           | 4 (0.9)      | 1 (0.2)      | 15 (5)    | 2 (<1)    | 8 (2)     | 25 (4)           |
| Diarrhea                 | 2 (3.9)    | 13 (23.6) | 12 (23.5) | 17 (32.1) | 9 (16.7)   | 2 (7.7)    | 9 (31.0)  | 10 (35.7)   | 9 (32.1)    | 65 (13.8)    | 54 (11.5)    | 12.2      | 19.5      | 20.4      | 3.2              |
| Nausea                   | 3 (5.9)    | 11 (20)   | 11 (21.6) | 21 (39.6) | 16 (29.6)  | 2 (7.7)    | 7 (24.1)  | 11 (39.3)   | 10 (35.7)   | 104 (22.1)   | 84 (17.9)    | 11.9      | 15.9      | 22.2      | 1.6              |
| Decreased Appetite       | 1 (2.0)    | 11 (20)   | 13 (25.5) | 10 (18.9) | 3 (5.6)    | 0          | 4 (13.8)  | 6 (21.4)    | 8 (28.6)    | 42 (8.9)     | 25 (5.3)     | 29 (9)    | 36 (11)   | 35 (10)   | 5 (<1)           |
| Vomiting                 | 1 (2)      | 4 (7.3)   | 8 (15.7)  | 14 (26.4) | 5 (9.3)    | 1 (3.8)    | 5 (17.2)  | 5 (17.9)    | 5 (17.9)    | 46 (9.8)     | 39 (8.3)     | 4.9       | 8.2       | 8.3       | 1.1              |
| Headache                 | 2 (3.9)    | 2 (3.6)   | 1 (2)     | 5 (9.4)   | 1 (1.9)    | 2 (7.7)    | 2 (6.9)   | 6 (21.4)    | 5 (17.9)    | NR           | NR           | NR        | NR        | NR        | NR               |
| Dyspepsia                | 0          | 1 (1.8)   | 6 (11.8)  | 2 (3.8)   | 2 (3.7)    | 0          | 5 (17.2)  | 3 (10.7)    | 3 (10.7)    | 43 (9.1)     | 31 (6.6)     | 18 (6)    | 27 (8)    | 26 (8)    | 13 (1)           |
| Abdominal Pain           | 1 (2.0)    | 1 (1.8)   | 0         | 3 (5.7)   | 1 (1.9)    | 1 (3.8)    | 1 (3.4)   | 5 (17.9)    | 1 (3.6)     | 24 (5.1)     | 24 (5.1)     | NR        | NR        | NR        | NR               |
| Dizziness                | 2 (3.9)    | 2 (3.6)   | 2 (3.9)   | 5 (9.4)   | 1 (1.9)    | 2 (7.7)    | 0         | 1 (3.6)     | 3 (10.7)    | NR           | NR           | NR        | NR        | NR        | NR               |
| Hypoglycemia (≤70 mg/dL) | 2 (3.9)    | 4 (7.3)   | 5 (9.8)   | 4 (7.5)   | 2 (3.7)    | 0          | 2 (6.9)   | 5 (17.9)    | 5 (17.9)    | NR           | NR           | NR        | NR        | NR        | NR               |
| Hypoglycemia (≤54 mg/dL) | NR         | NR        | NR        | NR        | NR         | 0          | 0         | 0           | 0*          | 8 (1.7)      | 2 (0.4)      | 6.7       | 5.5       | 6.5       | 15.0             |
| Severe hypoglycemia      | 0          | 0         | 0         | 0         | 0          | 0          | 0         | 0           | 0           | 1 (0.2)      | 0            | NR        | NR        | NR        | NR               |
| Cholecystitis            | 0          | 0         | 1 (2.0)   | 0         | 1 (1.9)    | 0          | 0         | 0           | 0           | 4 (0.9)      | 2 (0.4)      | 3 (<1)    | 1 (<1)    | 1 (<1)    | 4 (<1)           |

|                                |         |         |         |         |          |         |         |         |    |          |          |          |          |         |           |
|--------------------------------|---------|---------|---------|---------|----------|---------|---------|---------|----|----------|----------|----------|----------|---------|-----------|
| <b>Acute pancreatitis</b>      | 0       | 2 (3.6) | 0       | 0       | 0        | 02      | 0       | 0       | 0  | 2 (0.4)  | 3 (0.6)  | NR       | NR       | NR      | NR        |
| <b>Injection site reaction</b> | 2 (3.9) | 3 (5.5) | 4 (7.8) | 1 (1.9) | 6 (11.1) | 0       | 2 (6.9) | 2 (7.1) | 0  | 21 (4.5) | 1 (0.2)  | 1 (<1)   | 2 (<1)   | 1 (<1)  | 4 (<1)    |
| <b>Hypersensitivity</b>        | 5 (9.8) | 2 (3.6) | 2 (3.9) | 2 (3.8) | 0        | 1 (3.8) | 0       | 0       | 0  | 8 (1.7)  | 11 (2.3) | NR       | NR       | NR      | NR        |
| <b>Diabetic Retinopathy</b>    | 0       | 0       | 0       | 0       | 0        | NR      | NR      | NR      | NR | 0        | 0        | 5 (2) ‡† | 5 (2) ‡† | 4(1) ‡† | 15 (2) ‡† |

Frias 2020 has two 15-mg arms following two different dosing schedules. AE: adverse event, BL: baseline, CI: confidence interval, D/C: discontinuation, ETD: estimated treatment difference, N: number, NR: not reported, OR: odds ratio, PBO: placebo, REF: reference, SD: standard deviation, TEAE: treatment emergent adverse event, TZP: tirzepatide

\*Fatal TEAE

+\*\* Discontinuation from active treatment due to AE

‡†Diabetic retinopathy complications

## ***Safety Outcomes for Injectable Semaglutide and Empagliflozin***

### Injectable Semaglutide

In the SUSTAIN-6 CVOT, there was a greater incidence of AEs that led to study discontinuation in the pooled semaglutide versus pooled placebo group (13% vs. 6.7%, respectively;  $p=NR$ )(Table D4.10.). The rates of gastrointestinal AEs (nausea, vomiting, diarrhea) were greater in the semaglutide arm than placebo, in line with expectations of the GLP-1 RA class. Semaglutide carries an FDA warning label for pancreatitis; less than one percent of participants in either pooled arm experienced adjudicated acute pancreatitis ( $p=NR$ ). Semaglutide is contraindicated in patients with medullary thyroid carcinoma; neither treatment arm experienced this adverse event. There was little difference between arms in occurrence of malignant neoplasms.

### Empagliflozin

In the EMPA-REG OUTCOME CVOT, there was a significantly lower incidence of AEs that led to study discontinuation in the pooled empagliflozin versus placebo group (17.3% vs. 19.4%, respectively;  $p<.01$ )(Table D4.10.). The most frequent adverse events in the trial were urinary tract infection and genital infection (Table D4.10.). Among female study participants, those treated with empagliflozin experienced fewer rates of urinary tract infection than placebo (36.4% vs. 40.6%, respectively;  $p<.05$ ). Empagliflozin significantly increased the rate of genital infection versus placebo (6.4% vs. 1.8%). Within the empagliflozin treatment arm, female participants had twice the rate of genital infection versus male participants (10.0% vs. 5.0%).

**Table D4.7. Baseline Characteristics– NMA Linkage Studies<sup>38,113-115</sup>**

| Study                         |              | SUSTAIN-2   |             | PIONEER 2   |             |             | PIONEER 3   |             | HARMONY 3   |            |
|-------------------------------|--------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|
| Arm                           |              | SEM 1.0 mg  | SITA 100 mg | OSEM 14 mg  | EMPA 25 mg  | Total       | SEM 14 mg   | SITA 100 mg | PBO         | SITA 100mg |
| N                             |              | 409         | 407         | 411         | 410         | 821         | 465         | 467         | 101         | 302        |
| Age, y                        | Mean (SD)    | 56.0 (9.4)  | 54.6 (10.4) | 57 (10)     | 58 (10)     | 58 (10)     | 57 (10)     | 58 (10)     | 56.1 (10.0) | 54.3 (9.8) |
| Sex, n (%)                    | Men          | 205 (50)    | 208 (51)    | 206 (50.1%) | 209 (51.0%) | 415 (50.6%) | 247 (53.1%) | 238 (51.0%) | 50 (49.5)   | 139 (46.0) |
|                               | Women        | 204 (50)    | 199 (49)    | 205 (49.9)  | 201 (49.0)  | 406 (49.5)  | 218 (46.9)  | 229 (49.0)  | NR          | NR         |
| Diabetes Duration, y          | Mean         | 6.7         | 6.6         | 7.2         | 7.7         | 7.4         | 8.7         | 8.8         | 6.7         | 5.8        |
|                               | SD           | 5.6         | 5.1         | 5.8         | 6.3         | 6.1         | 6.1         | 6           | 6.6         | 4.8        |
| HbA1c, mean (SD)              | %            | 8.0 (0.9)   | 8.2 (0.9)   | 8.1 (0.9)   | 8.1 (0.9)   | 8.1 (0.9)   | 8.3 (0.9)   | 8.3 (0.9)   | 8.2 (0.9)   | 8.1 (0.8)  |
| Weight, kg                    | Mean         | 89.2        | 89.3        | 91.9        | 91.3        | 91.6        | 91.2        | 90.9        | 91.6        | 90.3       |
|                               | SD           | 20.7        | 19.7        | 20.5        | 20.1        | 20.3        | 21.7        | 21          | 19.3        | 19.1       |
| BMI, kg/ m <sup>2</sup>       | mean (SD)    | 32.5 (6.6)  | 32.5 (5.8)  | 32.9 (6.3)  | 32.8 (5.9)  | 32.8 (6.1)  | 32.3 (6.3)  | 32.5 (6.2)  | 32.8 (5.4)  | 32.5 (5.4) |
| Waist Circumference, cm       | Mean (SD)    | NR          | NR          | NR          | NR          | NR          | NR          | NR          | NR          | NR         |
| eGFR                          | Mean (SD)    | 97 (55-171) | 98 (53-194) | 96 (15)     | 95 (15)     | 95 (15)     | 95 (16)     | 96 (15)     | NR          | NR         |
| Metformin use, N (%)          | Yes          | 407 (100)   | 405 (100)   | 411 (100)   | 410 (100)   | 821 (100)   | 465 (100)   | 467 (100)   | NR          | NR         |
| Ethnicity, N (%)              | Hispanic     | 67 (16)     | 73 (18)     | 91 (22.1)   | 108 (26.3)  | 199 (24.2)  | 75 (16.1)   | 93 (19.9)   | 32 (31.7)   | 111 (36.8) |
|                               | Non-Hispanic | 342 (84)    | 334 (82)    | 320 (77.9)  | 302 (73.7)  | 622 (75.8)  | 390 (83.9)  | 374 (80.1)  | NR          | NR         |
| Race, N (%)                   |              |             |             |             |             |             |             |             |             |            |
| American Indian/Alaska Native |              | NR          | NR          | NR          | NR          | NR          | 5 (1.1)     | 6 (1.3)     | NR          | NR         |
| Black                         |              | 24 (6)      | 17 (4)      | 26 (6.3)    | 33 (8.0)    | 59 (7.2)    | 45 (9.7)    | 39 (8.4)    | 23 (22.8)   | 35 (11.6)  |

|              |          |          |            |            |            |            |            |           |            |
|--------------|----------|----------|------------|------------|------------|------------|------------|-----------|------------|
| <b>Asian</b> | 99 (24)  | 102 (25) | 28 (6.8)   | 21 (5.1)   | 49 (6.0)   | 61 (13.1)  | 59 (12.6)  | 5 (5.0)   | 20 (6.6)   |
| <b>White</b> | 279 (68) | 281 (69) | 355 (86.4) | 353 (86.1) | 708 (86.2) | 317 (68.2) | 333 (71.3) | 64 (63.4) | 225 (74.5) |

EMPA: empagliflozin, N: number, NR: not reported, OSEM: oral semaglutide, REF: reference, SD: standard deviation, SEM: semaglutide, y: years

**Table D4.8. Outcomes– NMA Linkage Studies<sup>38,113-115</sup>**

| Study                    |                      | SUSTAIN-2      |                |             | PIONEER-2    |            | PIONEER-3    |             | HARMONY 3 |             |
|--------------------------|----------------------|----------------|----------------|-------------|--------------|------------|--------------|-------------|-----------|-------------|
| Arm                      |                      | SEM 0.5 mg     | SEM 1.0 mg     | SITA 100 mg | OSEM 14 mg   | EMPA 25 mg | OSEM 14 mg   | SITA 100 mg | PBO       | SITA 100 mg |
| N                        |                      | 409            | 409            | 407         | 411          | 410        | 465          | 467         | 101       | 302         |
| Timepoint                |                      | 56 wks         |                |             | 52 wks       |            |              |             | 104 wks   |             |
| Glycaemia Endpoints      |                      |                |                |             |              |            |              |             |           |             |
| HbA1c, %                 | Mean, Change from BL | -1.3           | -1.6*          | -0.5*       | -1.3         | -0.9       | -1.2         | -0.7        | NR        | NR          |
|                          | ETD                  | -0.77          | -1.06          | NA          | -0.4         | REF        | -0.5         | REF         | NR        | NR          |
|                          | 95% CI (ETD)         | -0.92 to -0.62 | -1.21 to -0.91 | NA          | -0.5 to -0.3 | REF        | -0.6 to -0.3 | REF         | NR        | NR          |
|                          | p-value (ETD)        | <0.0001        | <0.0001        | REF         | <0.0001      | REF        | <0.001       | REF         | NR        | NR          |
| Lipid Levels             |                      |                |                |             |              |            |              |             |           |             |
| Triglycerides, mg/dL     | Change from BL       | NR             | NR             | NR          | -16.8        | -15.9      | -10.9        | -1.6        | -3.5*     | -13.2*      |
| Total Cholesterol, mg/dL | Change from BL       | NR             | NR             | NR          | -5.4         | 3.9        | -1.7         | 1.7         | -1.9*     | -3.5*       |
| HDL Cholesterol, mg/dL   | Change from BL       | NR             | NR             | NR          | 0.4          | 2.7        | 0.4          | 0           | 1.2*      | 1.2*        |
| LDL Cholesterol, mg/dL   | Change from BL       | NR             | NR             | NR          | -3.9         | 2.7        | 0            | 2.8         | -1.2*     | -1.9*       |
| Body Weight Endpoints    |                      |                |                |             |              |            |              |             |           |             |
| Weight, kg               | Change from BL       | -4.3           | -6.1           | -1.9        | -3.8         | -3.6       | -3.4         | -0.8        | -1.0*     | -0.86*      |

|                                      |                |                     |                      |            |                     |           |               |      |       |        |
|--------------------------------------|----------------|---------------------|----------------------|------------|---------------------|-----------|---------------|------|-------|--------|
|                                      | ETD            | -2.35               | -4.20                | NA         | -0.2                | REF       | -2.7          | REF  | NR    | NR     |
|                                      | 95% CI         | -3.06 to -1.63      | -4.91 to -3.49       | NA         | -0.9 to 0.5         | REF       | -3.3 to -2.1  | REF  | NR    | NR     |
|                                      | p-value        | <0.0001             | <0.0001              | REF        | 0.6231              | REF       | <0.001        | REF  | NR    | NR     |
| <b>Mean Waist Circumference, cm</b>  | Change from BL | -4.3                | -5.9                 | -2.2       | -3.5                | -2.9      | -2.6          | -0.4 | NR    | NR     |
|                                      | ETD            | -2.10               | -3.67                | NA         | -0.6                | REF       | -2.2          | REF  | NR    | NR     |
|                                      | 95% CI         | -2.91 to -1.29      | -4.48 to -2.87       | NA         | -1.4 to 0.2         | REF       | -3.0 to -1.4  | REF  | NR    | NR     |
|                                      | p-value        | <0.0001             | <0.0001              | REF        | 0.1488              | REF       | <0.001        | REF  | NR    | NR     |
| <b>Blood Pressure and Pulse Rate</b> |                |                     |                      |            |                     |           |               |      |       |        |
| <b>DBP, mmHg</b>                     | Change from BL | -2.0                | -1.9                 | -1.1       | -2                  | -2        | -2            | -1   | 0*    | 0.2*   |
|                                      | ETD            | -0.90               | -0.80                | NA         | 0                   | REF       | -1            | REF  | NR    | NR     |
|                                      | 95% CI         | -2.10 to 0.30       | -2.00 to 0.40        | NA         | -1 to 2             | REF       | -2 to 0       | REF  | NR    | NR     |
|                                      | p-value        | 0.14                | 0.19                 | REF        | 0.6551              | REF       | 0.28          | REF  | NR    | NR     |
| <b>SBP, mmHg</b>                     | Change from BL | -5.1                | -5.6                 | -2.3       | -4                  | -4        | -3            | -1   | 2.2*  | 0.2*   |
|                                      | ETD            | -2.78               | -3.32                | NA         | 0                   | REF       | -2            | REF  | NR    | NR     |
|                                      | 95% CI         | -4.59 to -0.97      | -5.13 to -1.52       | NA         | -2 to 2             | REF       | -4 to -1      | REF  | NR    | NR     |
|                                      | p-value        | 0.0026              | 0.0003               | REF        | 0.9371              | REF       | 0.01          | REF  | NR    | NR     |
| <b>Achieving HbA1C Targets</b>       |                |                     |                      |            |                     |           |               |      |       |        |
| <b>&lt;7%</b>                        | N (%)          | 282 (69) *          | 321 (78) *           | 148 (36) * | 214 (55.7)          | 149 (39)  | 53            | 31   | 15.5* | 31.6*  |
|                                      | OR (95% CI)    | 4.16 (3.02 to 5.74) | 7.92 (5.59 to 11.22) | REF        | 2.03 (1.50 to 2.74) | REF       | 22 (16 to 28) | REF  | NR    | NR     |
|                                      | p-value        | <0.0001             | <0.0001              | REF        | <0.0001             | REF       | <0.001        | REF  | NR    | NR     |
| <b>&lt;6.5%</b>                      | N (%)          | 215 (53) *          | 270 (66) *           | 83 (20) *  | 182 (47.4)          | 83 (21.7) | 32            | 14   | 7.2*  | 15.2 * |

|   |             |                     |                      |         |                     |          |               |     |    |    |
|---|-------------|---------------------|----------------------|---------|---------------------|----------|---------------|-----|----|----|
|   | OR (95% CI) | 4.39 (3.15 to 6.12) | 8.99 (6.36 to 12.72) | REF     | 3.36 (2.43 to 4.66) | REF      | 18 (13 to 24) | REF | NR | NR |
|   | p-value     | <0.0001             | <0.0001              | REF     | <0.0001             | REF      | <0.001        | REF | NR | NR |
| <5.7%   | N (%)       | NR                  | NR                   | NR      | NR                  | NR       | NR            | NR  | NR | NR |
|   | OR (95% CI) | NR                  | NR                   | NR      | NR                  | NR       | NR            | NR  | NR | NR |
|   | p-value     | NR                  | NR                   | NR      | NR                  | NR       | NR            | NR  | NR | NR |
| <b>Achieving bodyweight reduction Targets</b> |             |                     |                      |         |                     |          |               |     |    |    |
| ≥5%   | N (%)       | 188 (46)            | 254 (62)             | 75 (18) | NR                  | NR       | 34            | 12  | NR | NR |
|   | OR (95% CI) | 3.76 (2.72 to 5.19) | 7.47 (5.38 to 10.37) | REF     | NR                  | NR       | 22 (16 to 27) | REF | NR | NR |
|   | p-value     | <0.0001             | <0.0001              | REF     | NR                  | NR       | <0.001        | REF | NR | NR |
| ≥10 %   | N (%)       | 52 (13)             | 97 (24)              | 14 (3)  | 58 (15)             | 30 (7.8) | 11            | 3   | NR | NR |
|   | OR (95% CI) | 4.09 (2.26 to 7.40) | 8.85 (5.01 to 15.61) | REF     | 2.05 (1.28 to 3.28) | REF      | 8 (5 to 12)   | REF | NR | NR |
|   | p-value     | <0.0001             | <0.0001              | REF     | 0.0028              | REF      | <0.001        | REF | NR | NR |
| ≥15 %   | N (%)       | NR                  | NR                   | NR      | NR                  | NR       | NR            | NR  | NR | NR |
|   | OR (95% CI) | NR                  | NR                   | NR      | NR                  | NR       | NR            | NR  | NR | NR |
|   | p-value     | NR                  | NR                   | NR      | NR                  | NR       | NR            | NR  | NR | NR |

BL: baseline, CI: confidence interval, DBP: diastolic blood pressure, EMPA: empagliflozin, ETD: estimated treatment difference, N: number, NA: not applicable, NR: not reported, OR: odds ratio, OSEM: oral semaglutide, REF: reference, SBP: systolic blood pressure, SD: standard deviation, SEM: semaglutide, y: years, Lipid levels are NR, HbA1c target of <5.7% is NR, bodyweight target of >15% is NR.

\*Efficacy estimand



**Table D4.9. Safety– NMA Linkage Studies<sup>38,113-115</sup>**

| Study                                   | SUSTAIN-2  |             | PIONEER 2  |            | PIONEER 3  |             | HARMONY 3 |             |
|---|------------|-------------|------------|------------|------------|-------------|-----------|-------------|
| Arm                                     | SEM 1.0 mg | SITA 100 mg | OSEM 14 mg | EMPA 25 mg | OSEM 14 mg | SITA 100 mg | PBO       | SITA 100 mg |
| N                                       | 409        | 407         | 411        | 410        | 465        | 467         | 101       | 302         |
| Timepoint                               | 40 wks     |             | 52 wks     |            | 56 wks     |             | 104 wks   |             |
| Any AE                                  | NR         | NR          | 289 (70.5) | 283 (69.2) | 370 (79.6) | 388 (83.3)  | 79.2      | 79.1        |
| Any TEAE, n (%)                         | 292 (71)   | 292 (72)    | NR         | NR         | NR         | NR          | 20.8      | 17.9        |
| D/C Due to AE, n (%)                    | 39 (10)    | 12 (3)      | 44 (10.7)  | 18 (4.4)   | 54 (11.6)  | 24 (52.)    | 5         | 3.6         |
| D/C from Study Drug                     | NR         | NR          | NR         | NR         | NR         | NR          | NR        | NR          |
| Serious AE                              | 30 (7)     | 29 (7)      | 27 (6.6)   | 37 (9.0)   | 44 (9.5)   | 58 (12.4)   | 12.9      | 17.9        |
| Death                                   | 1 (1)      | 3 (1)       | 0          | 1 (0.2)    | 1 (0.2)    | 3 (0.6)     | NR        | NR          |
| Diarrhea                                | 53 (13)    | 29 (7)      | 38 (9.3)   | 13 (3.2)   | 57 (12.3)  | 37 (7.9)    | 10.9      | 8.6         |
| Nausea                                  | 72 (18)    | 30 (7)      | 81 (19.8)  | 10 (2.4)   | 70 (15.1)  | 32 (6.9)    | 10.9      | 6.6         |
| Decreased Appetite                      | 27 (7)     | 11 (3)      | 21 (5.1)   | 2 (0.5)    | 32 (6.9)   | 14 (3.0)    | NR        | NR          |
| Vomiting                                | 41 (10)    | 11 (3)      | 30 (7.3)   | 7 (1.7)    | 42 (9.0)   | 19 (4.1)    | NR        | NR          |
| Headache                                | 29 (7)     | 17 (4)      | NR         | NR         | 37 (8.0)   | 36 (7.7)    | NR        | NR          |
| Dyspepsia                               | 20 (5)     | 9 (2)       | NR         | NR         | 0          | 0           | NR        | NR          |
| Abdominal Pain                          | NR         | NR          | 5 (1.2)    | 0          | 2 (0.4)    | 2 (0.4)     | NR        | NR          |
| Dizziness                               | NR         | NR          | NR         | NR         | 1 (0.2)    | 0           | NR        | NR          |
| Hypoglycemia (plasma glucose ≤70 mg/dL) | NR         | NR          | 45         | 39         | 131 (28.2) | 112 (24.0)  | NR        | NR          |
| Hypoglycemia (plasma glucose ≤54 mg/dL) | NR         | NR          | 7 (1.7)    | 8 (2.0)    | 36 (7.7)   | 39 (8.4)    | 4 (4.0)   | 5 (1.7)     |
| Severe hypoglycemia                     | NR         | NR          | 1 (0.2)    | 1 (0.2)    | 1 (0.2)    | 4 (0.9)     | 0         | 0           |
| Cholecystitis                           | 1 (1)      | 0 (0)       | NR         | NR         | NR         | NR          | NR        | NR          |
| Acute pancreatitis                      | --         | --          | 1 (0.2)    | 1 (0.2)    | 3 (0.6)    | 1 (0.2)     | NR        | NR          |
| Injection site reaction                 | NR         | NR          | NA         | NA         | NA         | NA          | 2         | 1.7         |
| Hypersensitivity                        | NR         | NR          | NR         | NR         | NR         | NR          | NR        | NR          |
| Diabetic Retinopathy                    | 0          | 3 (1)       | 13 (3.2)   | 4 (1.0)    | 17 (3.7)   | 29 (6.2)    | NR        | NR          |

AE: adverse event, CI: confidence interval, D/C: discontinuation, EMPA: empagliflozin, N: number, NA: not applicable, NR: not reported, OR: odds ratio, OSEM: oral semaglutide, REF: reference, SD: standard deviation, SEM: semaglutide, TEAE: treatment emergent adverse event, y: years

**Table D4.10. CVOT Studies<sup>7,8</sup>**

| Study                                    |           | SUSTAIN-6   |              | EMPA-REG -OUTCOME |                |
|--|-----------|-------------|--------------|-------------------|----------------|
|  | Arms      | SEM 1mg     | PBO 1mg      | PBO               | EMPA (10/25mg) |
| N  |           | 822         | 825          | 2333              | 4687           |
|  | Timepoint | 109 wks     |              | 156 wks           |                |
| Baseline Characteristics                 |           |             |              |                   |                |
| Age, yr                                  |           | 64.7 (7.1)  | 64.4 (7.5)   | 63.2 (8.8)        | 63.1 (8.6)     |
| Male sex, N (%)                          |           | 518 (63)    | 507 (61.5)   | 1680 (72.0)       | 3336 (71.2)    |
| Weight, kg (SD)                          |           | 92.9 (21.1) | 91.9 (20.8)  | 86.6 (19.1)       | 86.2 (18.9)    |
| BMI, kg/m <sup>2</sup> (SD)              |           | 32.9 (6.2)  | 32.7 (6)     | 30.7 (5.2)        | 30.6 (5.3)     |
| Type 2 Diabetes                          |           |             |              |                   |                |
| Diabetes Duration, yr (SD)               |           | 14.1 (8.2)  | 13.2 (7.4)   | NR                | NR             |
| Hemoglobin, % (SD)                       |           | 8.7 (1.5)   | 8.7 (1.5)    | 8.08 (0.84)       | 8.07 (0.85)    |
| Race                                     |           |             |              |                   |                |
| White, n (%)                             |           | 691 (84.1)  | 676 (81.9)   | 1678 (71.9)       | 3403 (72.6)    |
| Asian, n (%)                             |           | 58 (7.1)    | 72 (8.7)     | 511 (21.9)        | 1006 (21.5)    |
| Black, n (%)                             |           | 54 (6.6)    | 59 (7.2)     | 120 (5.1)         | 237 (5.1)      |
| Ethnicity                                |           |             |              |                   |                |
| Hispanic or Latino, n (%)                |           | 124 (15.1)  | 137 (16.6)   | 418 (17.9)        | 847 (18.1)     |
| Antihyperglycemic Medication at Baseline |           |             |              |                   |                |
| Metformin, n (%)                         |           | 594 (72.3)  | 617 (74.8)   | 1734 (74.3)       | 3459 (73.8)    |
| Insulin, n (%)                           |           | 477 (58.0)  | 479 (58.1)   | 1135 (48.6)       | 2252 (48.0)    |
| Sulfonylurea, n (%)                      |           | 349 (42.5)  | 349 (42.3)   | 992 (42.5)        | 2014 (43.0)    |
| Cardiovascular Risk Factors              |           |             |              |                   |                |
| Systolic Blood Pressure (mmHg)           |           | 135.8 (17)  | 134.8 (17.5) | 135.8 (17.2)      | 135.3 (16.9)   |
| Diastolic Blood Pressure (mmHg)          |           | 76.9 (10.2) | 76.7 (10.2)  | 76.8 (10.1)       | 76.6 (9.7)     |
| LDL Cholesterol                          |           | 83.3 (41.2) | 83.6 (45.9)  | 84.9 (35.3)       | 85.9 (36.0)    |
| Never Smoked, n (%)                      |           | 364 (44.3)  | 348 (42.2)   | 957 (41.0)        | 1925 (41.1)    |
| History of Cardiovascular Disease, N (%) |           |             |              |                   |                |

|  |              |                     |            |                     |                      |
|--|--------------|---------------------|------------|---------------------|----------------------|
| <b>Ischemic Heart Disease</b>  |              | 495 (60.2)          | 496 (60.1) | 1763 (75.6)         | 3545 (75.6)          |
| <b>Myocardial Infarction</b>   |              | 264 (32.1)          | 275 (33.3) | 1083 (46.4)         | 2190 (46.7)          |
| <b>Heart Failure</b>   |              | 180 (21.9)          | 206 (25)   | 244 (10.5)          | 462 (9.9)            |
| <b>Ischemic Stroke</b>   |              | 89 (10.8)           | 109 (13.2) | 553 (23.7)          | 1084 (23.1)          |
| <b>Hemorrhagic Stroke</b>  |              | 24 (2.9)            | 29 (3.5)   |                     |                      |
| <b>Hypertension</b>  |              | 771 (93.8)          | 760 (92.1) | NR                  | NR                   |
| <b>Renal Function (Estimated glomerular filtration rate)</b>   |              |                     |            |                     |                      |
| <b>≥90 mL/min/1.73m<sup>2</sup> (normal)</b>   |              | 246 (29.9)          | 252 (30.5) | 488 (20.9)          | 1050 (22.4)          |
| <b>60 to &lt;90 mL/min/1.73m<sup>2</sup> (mild)</b>  |              | 357 (43.4)          | 346 (41.9) | 1238 (53.1)         | 2423 (51.7)          |
| <b>&lt;60 mL/min/1.73m<sup>2</sup> (moderate to end stage)</b>   |              | 219 (26.6)          | 227 (27.5) | 607 (26.0)          | 1212 (25.9)          |
| <b>Outcomes</b>  |              |                     |            |                     |                      |
| <b>Composite Outcome (CV Causes, Non-fatal MI, or Non-fatal stroke)</b>  | n (%)        | 108 (6.6)           | 146 (8.9)  | 282 (12.1)          | 490 (10.5)           |
|  | HR (95%CI)   | 0.74 (0.58 to 0.95) |            | 0.86 (0.74 to 0.99) |                      |
|  | p-value, NON | <0.001              | REF        | <.001               | REF                  |
|  | p-value, SUP | 0.02                | REF        | 0.04                | REF                  |
| <b>Expanded Composite Outcome (Death from CV Causes, Non-fatal MI, Non-fatal Stroke, Revascularization, Hospitalization, HF)</b> | n (%)        | 199 (12.1)          | 264 (16.0) | 333 (14.3)          | 599 (12.8)           |
|  | HR (95%CI)   | 0.74 (0.62 to 0.89) |            | 0.89 (0.78 to 1.01) |                      |
|  | p-value, NON | 0.002               | REF        | <.001               | REF                  |
|  | p-value, SUP | NA                  | NA         | 0.08                | REF                  |
| <b>All Cause Death, Non-fatal MI, or Non-fatal Stroke</b>  | n (%)        | 122 (7.4)           | 158 (9.6)  | NR                  | NR                   |
|  | HR (95%CI)   | 0.77 (0.61 to 0.97) |            | NR                  | NR                   |
|  | p-value      | 0.03                | REF        | NR                  | NR                   |
| <b>From Any Cause</b>  | n (%)        | 62 (3.8)            | 60 (3.6)   | 194 (8.3)           | 269 (5.7)            |
|  | HR (95%CI)   | 1.05 (0.74 to 1.50) |            | 0.68 (0.57 to 0.82) |                      |
|  | p-value      | 0.79                | REF        | <.001               | REF                  |
| <b>From Cardiovascular Cause</b>   | n (%)        | 44 (2.7)            | 46 (2.8)   | 137 (5.9)           | 172 (3.7)            |
|  | HR (95%CI)   | 0.98 (0.65 to 1.48) |            | 0.62 (0.49 to 0.77) |                      |
|  | p-value      | 0.92                | REF        | <.001               | REF                  |
| <b>Non-fatal MI</b>  |              | n (%)               | 47 (2.9)   | 64 (3.9)            | 121 (5.2)* 213 (4.5) |

|  |            |                     |            |                     |             |
|--|------------|---------------------|------------|---------------------|-------------|
|  | HR (95%CI) | 0.74 (0.51 to 1.08) |            | 0.87 (0.70-1.09)    |             |
|  | p-value    | 0.12                | REF        | 0.22                | REF         |
| <b>Non-fatal Stroke</b>                    | n (%)      | 27 (1.6)            | 44 (2.7)   | 60 (2.6)            | 150 (3.2)   |
|  | HR (95%CI) | 0.61 (0.38 to 0.99) |            | 1.24 (0.92 to 1.67) |             |
|  | p-value    | 0.04                | REF        | 0.16                | REF         |
|  |            |                     |            |                     |             |
| <b>Hospitalization for Unstable Angina</b> | n (%)      | 22 (1.3)            | 27 (1.6)   | 66 (2.8)            | 133 (2.8)   |
|  | HR (95%CI) | 0.82 (0.47 to 1.44) |            | 0.99 (0.74 to 1.34) |             |
|  | p-value    | 0.49                | REF        | 0.97                | REF         |
|  |            |                     |            |                     |             |
| <b>Revascularization</b>                   | n (%)      | 83 (5.0)            | 126 (7.6)  | 186 (8.0)           | 329 (7.0)   |
|  | HR (95%CI) | 0.65 (0.50 to 0.86) |            | 0.86 (0.72 to 1.04) |             |
|  | p-value    | 0.003               | REF        | 0.11                | REF         |
|  |            |                     |            |                     |             |
| <b>Hospitalization for Heart Failure</b>   | n (%)      | 59 (3.6)            | 54 (3.3)   | 95 (4.1)            | 126 (2.7)   |
|  | HR (95%CI) | 1.11 (0.77 to 1.61) |            | 0.65 (0.50 to 0.85) |             |
|  | p-value    | 0.57                | REF        | 0.002               | REF         |
|  |            |                     |            |                     |             |
| <b>Retinopathy Complications</b>           | n (%)      | 50 (3.0)            | 29 (1.8)   | 29 (1.2)            | 41 (0.9)    |
|  | HR (95%CI) | 1.76 (1.11 to 2.78) |            | 0.69 (0.43 to 1.12) |             |
|  | p-value    | 0.02                | REF        | 0.134               | REF         |
|  |            |                     |            |                     |             |
| <b>New or worsening nephropathy</b>        | n (%)      | 62 (3.8)            | 100 (6.1)  | 388 (18.8)          | 525 (12.7)  |
|  | HR (95%CI) | 0.64 (0.46 to 0.88) |            | 0.61 (0.53 to 0.70) |             |
|  | p-value    | 0.005               | REF        | <0.001              | REF         |
|  |            |                     |            |                     |             |
| <b>Adverse Events, n (%)</b>               |            |                     |            |                     |             |
| <b>Adverse Events</b>                      |            | 732 (89.1)          | 736 (89.2) | 2139 (91.7)         | 4230 (90.2) |
| <b>Serious Adverse Event</b>               |            | 276 (33.6)          | 298 (36.1) | 592 (25.4)          | 1100 (23.5) |
| <b>Severe Adverse Events</b>               |            | 207 (25.2)          | 194 (23.5) | 988 (42.3)          | 1789 (38.2) |
| <b>Leading to D/C</b>                      |            | 119 (14.5)          | 63 (7.6)   | 453 (19.4)          | 813 (17.3)  |
| <b>Gastrointestinal Disorder</b>           |            | 430 (52.3)          | 290 (35.2) | NR                  | NR          |
| <b>Nausea</b>                              |            | 151 (18.4)          | 87 (10.5)  | NR                  | NR          |
| <b>Vomiting</b>                            |            | 122 (14.8)          | 34 (4.1)   | NR                  | NR          |
| <b>Diarrhea</b>                            |            | 151 (18.4)          | 87 (10.5)  | NR                  | NR          |

|  |                 |            |            |            |            |
|--|-----------------|------------|------------|------------|------------|
| <b>Gallbladder Disorder</b>                          |                 | 26 (3.2)   | 23 (2.8)   | NR         | NR         |
| <b>Cholelithiasis</b>                                |                 | 17 (2.1)   | 12 (1.5)   | NR         | NR         |
| <b>Acute Cholecystitis</b>                           |                 | 0          | 2 (0.2)    | NR         | NR         |
| <b>Neoplasm</b>                                      |                 | 89 (10.8)  | 69 (8.4)   | NR         | NR         |
| <b>Benign</b>  |                 | 54 (6.6)   | 34 (4.1)   | NR         | NR         |
| <b>Malignancy, any</b>                               |                 | 40 (4.9)   | 35 (4.2)   | NR         | NR         |
| <b>Malignancy, pancreatic</b>                        |                 | 1 (0.1)    | 2 (0.2)    | NR         | NR         |
| <b>Other</b>   |                 |            |            |            |            |
| <b>Severe or symptomatic hypoglycemic event</b>      |                 | 178 (21.7) | 173 (21.0) | NR         | NR         |
| <b>Acute renal failure</b>                           |                 | 23 (2.8)   | 35 (4.2)   | 155 (6.6)  | 256 (5.2)  |
| <b>Allergic reaction</b>                             |                 | 49 (6.0)   | 57 (6.9)   | NR         | NR         |
| <b>Injection Site Reaction</b>                       |                 | 9 (1.1)    | 12 (1.5)   | NR         | NR         |
| <b>Cardiac disorder</b>                              |                 | 150 (18.2) | 173 (21.0) | NR         | NR         |
| <b>Atrial Fibrillation</b>                           |                 | 23 (2.8)   | 26 (3.2)   | NR         | NR         |
| <b>Acute Pancreatitis</b>                            |                 | 3 (0.4)    | 9 (1.1)    | NR         | NR         |
| <b>Event Consistent with Urinary Tract Infection</b> | Total           | NR         | NR         | 423 (18.1) | 842 (18)   |
|  | Male Patients   | NR         | NR         | 158 (9.4)  | 350 (10.5) |
|  | Female Patients | NR         | NR         | 265 (40.6) | 492 (36.4) |
| <b>Complicated Urinary Tract Infection</b>           |                 | NR         | NR         | 41 (1.8)   | 82 (1.7)   |
| <b>Event Consistent with Genital Infection</b>       | Total           | NR         | NR         | 42 (1.8)   | 301 (6.4)  |
|  | Male Patients   | NR         | NR         | 25 (1.5)   | 166 (5.0)  |
|  | Female Patients | NR         | NR         | 17 (2.6)   | 135 (10.0) |
| <b>Acute Kidney Failure</b>                          |                 | 23 (2.8)   | 35 (4.2)   | 155 (6.6)  | 246 (5.2)  |
| <b>Acute Kidney Injury</b>                           |                 | NR         | NR         | 37 (1.6)   | 45 (1.0)   |
| <b>Diabetic Ketoacidosis</b>                         |                 | NR         | NR         | 1 (<0.1)   | 4 (0.1)    |
| <b>Intermediate Outcomes at Week 104</b>             |                 |            |            |            |            |
| <b>HbA1c Change from baseline, %</b>                 |                 | -1.4       | -0.4       | -0.1       | -0.6†      |
| <b>Body Weight CFB, kg</b>                           |                 | -4.9       | -0.5       | -0.8       | -3†        |
| <b>SBP CFB, mmHg</b>                                 |                 | -5.37      | -2.78      | -0.8       | -4.1       |

|   |       |       |       |       |
|---|-------|-------|-------|-------|
| <b>DBP CFB, mmHg</b>                        | -1.57 | -1.71 | -1.5‡ | -2.2‡ |
| <b>Total Cholesterol, Ratio to Baseline</b> | 0.97  | 0.99  | NR    | NR    |
| <b>LDL Cholesterol, Ratio to Baseline</b>   | 0.97  | 0.99  | 1.03  | 1.05  |
| <b>HDL Cholesterol, Ratio to Baseline</b>   | 1.01  | 0.97  | 1.01  | 1.05  |
| <b>Triglycerides, Ratio to Baseline</b>     | 0.92  | 0.98  | NR    | NR    |

CI: confidence interval, CFB: change from baseline, CV: cardiovascular, DBP: diastolic blood pressure, HF: heart failure, HR: hazard ration, N: number, NR: not reported, REF: reference, SBP: systolic blood pressure, SD: standard deviation, y: years

\*Nonfatal myocardial infarction excluding silent myocardial infarction

†Outcomes for EMPA 25 mg

‡Digitized and calculated by ICER staff

**Table D4.11. CVOT Subgroups<sup>7,8</sup>**

| CVOT Subgroups    |                     |                           |          |                            |       |
|-------------------|---------------------|---------------------------|----------|----------------------------|-------|
| Study             |                     | SUSTAIN-6                 |          | EMPA-REG -OUTCOME          |       |
| Arm               |                     | SEM 1 mg                  | PBO 1 mg | PBO                        | EMPA  |
| N                 |                     | 822                       | 825      | 2333                       | 4687  |
| Timepoint         |                     | 109 wks                   |          | 156 wks                    |       |
| Composite Outcome |                     |                           |          |                            |       |
| BMI (kg/m²)       | <30                 | 6.2                       | 8.3      | 7.57                       | 10.13 |
|                   | HR: 95% CI; p-value | 0.58 (0.39 to 0.87); 0.16 |          | 0.74 (0.60 to 0.90)); 0.06 |       |
|                   | >30                 | 6.6                       | 7.7      | 9.05                       | 9.08  |
|                   | HR: 95% CI; p-value | 0.84 (0.61 to 1.16); 0.16 |          | 0.98 (0.80 to 1.21); 0.06  |       |
| Race              | Asian               | 6.6                       | 11.2     | 0.11                       | 0.07  |
|                   | HR: 95% CI; p-value | 0.58 (0.25 to 1.34); 0.88 |          | 0.66 (0.48 to 0.95); 0.09  |       |
|                   | Black/AA            | 4.6                       | 6.2      | 0.12                       | 0.16  |
|                   | HR: 95% CI; p-value | 0.72 (0.23 to 2.28); 0.88 |          | 1.48 (0.80 to 2.72)); 0.09 |       |
|                   | White               | 6.7                       | 8.7      | 0.12                       | 0.10  |
|                   | HR: 95% CI; p-value | 0.76 (0.58 to 1.00); 0.88 |          | 0.88 (0.74 to 1.04); 0.09  |       |
| Ethnicity         | Hispanic            | 5.1                       | 7.5      | 8.03                       | 12.1  |
|                   | HR: 95% CI; p-value | 0.67 (0.33 to 1.36); 0.80 |          | 0.63 (0.44 to 0.90); 0.07  |       |
|                   | Non                 | 6.8                       | 8.7      | 8.31                       | 9.13  |
|                   | HR: 95% CI; p-value | 0.74 (0.57 to 0.96); 0.80 |          | 0.91 (0.77 to 1.07); 0.07  |       |
| Chronic HF        | No                  | 5.4                       | 8.2      | NR                         | NR    |
|                   | HR: 95% CI; p-value | 0.64 (0.48 to 0.86); 0.09 |          | NR                         | NR    |
|                   | Yes                 | 12.3                      | 11.8     | NR                         | NR    |
|                   | HR: 95% CI; p-value | 1.03 (0.64 to 1.66); 0.09 |          | NR                         | NR    |
| CVD Status        | Established         | 5.4                       | 9.9      | NR                         | NR    |
|                   | HR: 95% CI; p-value | 0.72 (0.55 to 0.93); 0.49 |          | NR                         | NR    |
|                   | Risk                | 3.4                       | 3.4      | NR                         | NR    |
|                   | HR: 95% CI; p-value | 1.00 (0.41 to 2.46); 0.49 |          | NR                         | NR    |

|                                       |                     |                            |      |                             |       |
|---------------------------------------|---------------------|----------------------------|------|-----------------------------|-------|
| eGFR <60<br>mL/min/1.73m <sup>2</sup> | No                  | 5.3                        | 7.9  | NR                          | NR    |
|                                       | HR: 95% CI; p-value | 0.67 (0.48 to 0.92)); 0.98 |      | NR                          | NR    |
|                                       | Yes                 | 9.6                        | 11.3 | 6.13                        | 6.89  |
|                                       | HR: 95% CI; p-value | 0.84 (0.57 to 1.25)); 0.37 |      | 0.88 (0.69 to 1.13); 0.20   |       |
| CVD Death                             |                     |                            |      |                             |       |
| BMI (kg/m <sup>2</sup> )              | <30                 | NR                         | NR   | 14.36                       | 28.49 |
|                                       | HR: 95% CI; p-value | NR                         | NR   | 0.50 (0.37 to 0.68)*; 0.05  |       |
|                                       | >30                 | NR                         | NR   | 20.6                        | 26.17 |
|                                       | HR: 95% CI; p-value | NR                         | NR   | 0.78 (0.56 to 1.08)*; 0.05  |       |
| Ethnicity                             | Hispanic            | NR                         | NR   | 14.93                       | 22.32 |
|                                       | HR: 95% CI; p-value | NR                         | NR   | 0.53 (0.32 to 0.88)); 0.49  |       |
|                                       | Non                 | NR                         | NR   | 17.54                       | 27.2  |
|                                       | HR: 95% CI; p-value | NR                         | NR   | 0.64 (0.50 to 0.83); 0.49   |       |
| eGFR <60<br>mL/min/1.73m <sup>2</sup> | No                  | NR                         | NR   | NR                          | NR    |
|                                       | HR: 95% CI; p-value | NR                         | NR   | NR                          | NR    |
|                                       | Yes                 | NR                         | NR   | 12.64                       | 16.16 |
|                                       | HR: 95% CI; p-value | NR                         | NR   | 0.78 (0.54 to 1.12)2); 0.15 |       |

AA: African American, BL: baseline, CI: confidence interval, DBP: diastolic blood pressure, EMPA: empagliflozin, ETD: estimated treatment difference, N: number, NR: not reported, OR: odds ratio, PBO: placebo, REF: reference, SBP: systolic blood pressure, SD: standard deviation, SEM: semaglutide

\*p=0.05 for interaction. All other tests for interaction were non-significant.

†Efficacy estimand



**Table D4.12. SURPASS-4 CV and Death Outcomes<sup>34</sup>**

| Study                               | SURPASS-4 CV Outcomes |           |           |                      |                  |
|-------------------------------------|-----------------------|-----------|-----------|----------------------|------------------|
| Arms                                | TZP 5 mg              | TZP 10 mg | TZP 15 mg | All TZP              | Insulin Glargine |
| N                                   | 329                   | 328       | 338       | 995                  | 1000             |
| Timepoint                           | 104 weeks             |           |           |                      |                  |
| MACE-4                              | 19 (6)                | 17 (5)    | 11 (3)    | 47 (5)               | 62 (6)           |
| HR; 95% CI                          | --                    | --        | --        | 0.74 (0.51 to 1.08)* |                  |
| CV Death                            | 10 (3)                | 1 (<1)    | 5 (2)     | 16 (2)               | 21 (2)           |
| MI                                  | 7 (2)                 | 9 (3)     | 3 (<1)    | 19 (2)               | 21 (2)           |
| Hospitalization for unstable angina | 0                     | 2 (<1)    | 2 (<1)    | 4 (<1)               | 8 (<1)           |
| Stroke                              | 5 (2)                 | 5 (2)     | 1 (<1)    | 11 (<1)              | 13 (<1)          |
| Other MACE                          |                       |           |           |                      |                  |
| Coronary Interventions              | 10 (3)                | 11 (3)    | 8 (2)     | 29 (3)               | 37 (4)           |
| Transient Ischemic Attack           | 0                     | 2 (<1)    | 1 (<1)    | 3 (<1)               | 0                |
| Hospitalization for HF              | 1 (<1)                | 1 (<1)    | 2 (<1)    | 4 (<1)               | 0                |
| HR; 95% CI                          | --                    | --        | --        | --                   | --               |
| Death                               | 15 (5)                | 2 (<1)    | 8 (2)     | 25 (3)               | 35 (4)           |
| HR; 95% CI                          | --                    | --        | --        | 0.70 (0.42 to 1.17)* |                  |
| CV Death                            | 4 (1)                 | 0         | 2 (<1)    | 6 (<1)               | 9 (<1)           |
| Undetermined                        | 6 (2)                 | 1 (<1)    | 3 (<1)    | 10 (1)               | 12 (1)           |
| Non-CV                              | 5 (2)                 | 1 (<1)    | 3 (<1)    | 9 (<1)               | 14 (1)           |

CI: confidence interval, CV: cardiovascular, HF: heart failure, HR: hazard ration, MI: myocardial infarction, TZP: tirzepatide

\*Point estimate and 95%CI of hazard ratio comparing pooled TZP versus insulin

## D5. Ongoing Studies

Figure D5.1. Ongoing Studies

| Title / Trial Sponsor  | Study Design                                      | Comparators  | Patient Population  | Primary Outcomes   | Estimated Completion Dates |
|--|---|--|---|--|----------------------------|
| <b>A Study of Tirzepatide (LY3298176) Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes (SURPASS-CVOT)</b> | Phase 3, double-blind, randomized<br><br>N=12,500 | Arm 1: tirzepatide (SC)<br><br>Arm 2: Dulaglutide (SC)   | <u>Inclusion:</u><br>Have a diagnosis of T2DM<br><br>Have confirmed atherosclerotic cardiovascular disease<br><br>HbA1c $\geq 7.0\%$ to $\leq 10.5\%$<br><br>BMI $\geq 25$ kg/m <sup>2</sup><br><br><u>Exclusion:</u><br>Type 1 diabetes<br><br>MACE in the last 60 days<br><br>History of severe hypoglycemia<br>History of pancreatitis | Time to first occurrence of death from CV causes, MI, or stroke (MACE-3) | October 2024               |
| <b>A Study of Tirzepatide (LY3298176) in Participants with Type 2 Diabetes on Metformin with or Without Sulfonylurea (SURPASS-AP-Combo)</b>            | Phase 3, open-label<br><br>N=917                  | Arm 1: Tirzepatide 5 mg SC<br>Arm 2: Tirzepatide 10 mg SC<br>Arm 3: Tirzepatide 15 mg SC<br>Arm 4: Insulin glargine (SC) | <u>Inclusion:</u><br>Have a diagnosis of T2DM Type 2 diabetes mellitus<br><br>Stable metformin with or without a sulfonylurea for at least 2 months<br><br>Are insulin-naïve (except for the use of insulin for treatment of gestational diabetes or short-term use [ $\leq 14$ consecutive days] for acute conditions)                   | Mean change from baseline in HbA1c (10 mg and 15 mg)                     | November 2021              |

| Title / Trial Sponsor  | Study Design   | Comparators   | Patient Population  | Primary Outcomes  | Estimated Completion Dates |
|--|--|---|---|---|----------------------------|
|  |  |   | <p>HbA1c <math>\geq 7.5\%</math> to <math>\leq 11.0\%</math> at screening</p> <p>Stable weight (<math>\pm 5\%</math>) <math>\geq 3</math> months</p> <p>BMI <math>\geq 23</math> kg/m<sup>2</sup></p> <p><u>Exclusion:</u><br/>Type 1 diabetes mellitus</p> <p>Have history of chronic or acute pancreatitis</p> <p>Have history of proliferative diabetic retinopathy; or diabetic maculopathy; or non-proliferative diabetic retinopathy that requires acute treatment</p> <p>Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the three months</p> |   |                            |
| <b>A Study of Tirzepatide (LY3298176) Versus Insulin Lispro (U100) in Participants with Type 2 Diabetes Inadequately Controlled on Insulin Glargine (U100) With or Without Metformin (SURPASS-6)</b> | <p>Phase 3, randomized, open-label</p> <p>N=1182</p> | <p>Arm 1: Tirzepatide 5 mg SC + insulin (U100)</p> <p>Arm 2: Tirzepatide 10 mg SC + insulin (U100)</p> <p>Arm 3: Tirzepatide 15 mg SC + insulin (U100)</p> <p>Arm 4: Insulin glargine (SC) + insulin (U100)</p> | <p><u>Inclusion:</u><br/>Have been diagnosed with T2DM</p> <p>Have HbA1c between <math>\geq 7.5\%</math> and <math>\leq 11\%</math></p> <p>Have been treated for at least 90 days prior to day of screening with once or twice daily basal insulin with or without stable dose of metformin <math>\geq 1500</math> mg/day and up to maximum approved dose per country specific approved label, sulfonylureas or dipeptidyl peptidase 4 inhibitors</p>   | Change from baseline in HBA1C (pooled doses) at week 52 | November 2022              |

| Title / Trial Sponsor  | Study Design  | Comparators  | Patient Population   | Primary Outcomes   | Estimated Completion Dates |
|--|---|--|--|--|----------------------------|
|  |   |  | <p>Be of stable weight (<math>\pm 5\%</math>) for at least 90 days</p> <p>BMI <math>\geq 23</math> (kg/m<sup>2</sup>) and <math>\leq 45</math> kg/m<sup>2</sup> at screening</p> <p><u>Exclusion:</u><br/>Type 1 diabetes mellitus</p> <p>Chronic or acute pancreatitis any time prior to study entry</p> <p>Proliferative diabetic retinopathy or diabetic macular edema or non-proliferative diabetic retinopathy requiring immediate or urgent treatment</p> <p>Disorders associated with slowed emptying of the stomach, have had any stomach surgeries for the purpose of weight loss, or are chronically taking drugs that directly affect gastrointestinal motility</p> <p>Heart attack, stroke, or hospitalization for congestive heart failure in the past two months</p> |  |                            |
| <b>A Study of Tirzepatide (LY3298176) in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight (SURMOUNT-2)</b> | Phase 3 randomized, double-blind, placebo controlled<br><br>N=900 | Arm 1: Tirzepatide 10 mg SC + insulin (Uu100)<br>Arm 2: Tirzepatide 15 mg SC<br>Arm 3: placebo | <p><u>Inclusion</u><br/>Have Type 2 Diabetes (T2DM) with HbA1c <math>\geq 7\%</math> to <math>\leq 10\%</math> at screening, on stable therapy for the last 3 months prior to screening</p> <p>Have a BMI of <math>\geq 27</math> kg/m<sup>2</sup></p>   | Percent change from randomization in body weight and percentage of patients who achieve $>5\%$ | June 19, 2023              |

| Title / Trial Sponsor | Study Design | Comparators | Patient Population  | Primary Outcomes                          | Estimated Completion Dates |
|-----------------------|--------------|-------------|---|---|----------------------------|
|                       |              |             | <p>Are overweight or have obesity</p> <p>Have a history of at least one self-reported unsuccessful dietary effort to lose body weight</p> <p>Are at least 18 years of age and age of majority per local laws and regulations</p> <p><u>Exclusion</u></p> <p>Have Type 1 diabetes mellitus, history of ketoacidosis or hyperosmolar state/coma or any other types of diabetes except T2DM</p> <p>Have at least 2 confirmed fasting self-monitoring blood glucose (SMBG) values &gt;270 mg/dL (on two nonconsecutive days) prior to Visit 3</p> <p>Have proliferative diabetic retinopathy OR diabetic macular edema OR non-proliferative diabetic retinopathy that requires acute treatment</p> <p>Have self-reported change in body weight &gt;5 kg within 3 months prior to screening</p> <p>Have had a history of chronic or acute pancreatitis</p> | body weight reduction from randomization. |                            |

BMI: body mass index, CV: cardiovascular, HbA1c: hemoglobin A1c, kg: kilogram, MACE-3: 3-point MACE, mg: milligram, MI: myocardial infarction, N: number, SC: subcutaneous, T2DM: type 2 diabetes mellitus

Source: [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (NOTE: studies listed on site include both clinical trials and observational studies)

## D6. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessments conducted by the National Institute for Health and Care Excellence (NICE) on tirzepatide summarized below. We also identified two meta-analyses that include empagliflozin and subcutaneous injectable semaglutide in its analyses. All reports are summarized below.

### NICE Technology Assessments

#### [Tirzepatide for Treating Type 2 Diabetes](#)

NICE is currently conducting an appraisal of the clinical and cost-effectiveness of tirzepatide for treating type 2 diabetes. The expected publication date is to be confirmed.

***Salsali, A. (2016). "Cardiovascular safety of empagliflozin in patients with type 2 diabetes: a meta-analysis of data from randomized placebo-controlled trials"<sup>116</sup>***

This meta-analysis assessed the effect on empagliflozin on cardiovascular risk in patients with type 2 diabetes across eight placebo-controlled trials. Using data from all available empagliflozin (EMPA) trials greater than 12 weeks duration, the primary endpoint of this analysis was a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for unstable angina (MACE-4). The secondary endpoint was a composite of CV death, non-fatal MI and non-fatal stroke (MACE-3). Across all trials, 3835 patients were assigned to placebo, 3629 to EMPA 10 mg and 3828 to EMPA 25 mg with an average age of 61 and 65% of patients identifying as male. Baseline characteristics were generally similar across all arms. For pooled EMPA, patients had a reduced risk in MACE-4 versus placebo (HR 0.86; CI: 0.76 to 0.98) and MACE-3 (HR: 0.84; CI: 0.73 to 0.96). Similar results were seen for EMPA 10 mg alone and 25 mg alone.

***Shi, F. (2018) Efficacy and Safety of Once-Weekly Semaglutide for the Treatment of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials<sup>117</sup>***

A systematic review and meta-analysis were conducted to assess the efficacy and safety of once weekly injectable semaglutide in adult patients with T2DM. Of the 457 initial studies, nine studies met the inclusion criteria, evaluating a total of 9,773 patients. The outcomes of interest in this evaluation included glycemic control, weight control, blood pressure, pulse rate, and safety. Patients assigned to semaglutide had a significant decrease in HbA1c levels compared to other therapies (weight mean difference [WMD]: -0.93; CI: -1.24 to -0.62;  $p < 0.001$ ) although there was significant heterogeneity ( $I^2$ : 92.6%). Semaglutide also significantly reduced body weight (WMD: -3.47; CI: -3.96 to -2.98;  $p < 0.001$ ;  $I^2$ : 17.6) and systolic blood pressure (WMD: -0.29 mmHg; CI: -0.65 to 0.07;  $p = 0.0113$ ). Semaglutide significantly increased pulse rate compared to other therapies (WMD: 2.21 bpm; CI: 1.54 to 2.88;  $p < 0.0001$ ;  $I^2$ : 67.6). The safety profile was generally well

tolerated with no increased safety risk for semaglutide for adverse events (RR:1.04), serious AEs (RR: 0.93), or fatal AEs (RR: 0.90). There was a significant increase in premature treatment discontinuation associated with semaglutide (RR: 2.07; CI: 1.58 to 2.73;  $p<0.001$ ). The most common AEs were gastrointestinal events (42.9%) followed by nausea (18.1%) and diarrhea (14.0%).

## E. Long-Term Cost-Effectiveness: Supplemental Information

### E1. Detailed Methods

Table E1. Impact Inventory

| Sector                      | Type of Impact<br>(Add additional domains, as relevant)         | Included in This Analysis<br>from [...] Perspective? |                          | Notes on Sources (if<br>quantified), Likely<br>Magnitude & Impact<br>(if not) |
|-----------------------------|---|--|--------------------------|---|
|                             |   | Health Care<br>Sector                                | Societal                 |   |
| Formal Health Care Sector   |   |  |                          |   |
| Health<br>Outcomes          | Longevity effects   | X  | X                        |   |
|                             | Health-related quality of life effects                          | X  | X                        |   |
|                             | Adverse events  | X  | X                        |   |
| Medical Costs               | Paid by third-party payers                                      | X  | X                        |   |
|                             | Paid by patients out-of-pocket                                  | <input type="checkbox"/>                             | <input type="checkbox"/> |   |
|                             | Future related medical costs                                    | <input type="checkbox"/>                             | <input type="checkbox"/> |   |
|                             | Future unrelated medical costs                                  | <input type="checkbox"/>                             | <input type="checkbox"/> |   |
| Informal Health Care Sector |   |  |                          |   |
| Health-<br>Related Costs    | Patient time costs  | NA   | <input type="checkbox"/> |   |
|                             | Unpaid caregiver-time costs                                     | NA   | <input type="checkbox"/> |   |
|                             | Transportation costs  | NA   | <input type="checkbox"/> |   |
| Non-Health Care Sector      |   |  |                          |   |
| Productivity                | Labor market earnings lost                                      | NA   | X                        |   |
|                             | Cost of unpaid lost productivity due to illness                 | NA   | X                        |   |
|                             | Cost of uncompensated household production                      | NA   | <input type="checkbox"/> |   |
| Consumption                 | Future consumption unrelated to health                          | NA   | <input type="checkbox"/> |   |
| Social services             | Cost of social services as part of intervention                 | NA   | <input type="checkbox"/> |   |
| Legal/Criminal<br>Justice   | Number of crimes related to intervention                        | NA   | <input type="checkbox"/> |   |
|                             | Cost of crimes related to intervention                          | NA   | <input type="checkbox"/> |   |
| Education                   | Impact of intervention on educational achievement of population | NA   | <input type="checkbox"/> |   |
| Housing                     | Cost of home improvements, remediation                          | NA   | <input type="checkbox"/> |   |
| Environment                 | Production of toxic waste pollution by intervention             | NA   | <input type="checkbox"/> |   |
| Other                       | Other impacts (if relevant)                                     | NA   | <input type="checkbox"/> |   |

NA: not applicable

Adapted from Sanders et al.<sup>118</sup>



## Target Population

The target population of the model was patients with diabetes that were not controlled with first-line anti-hypoglycemic medication who were eligible for an add-on therapy such as tirzepatide, injectable semaglutide, or empagliflozin. Description of the included patient population, derived from the NHANES is included in the main report. We assume our patient population is eligible for add-on therapy to help control their diabetes. The three add-on (to background therapy) therapies we consider are: tirzepatide, 15 mg once weekly via subcutaneous injection; semaglutide (Ozempic®), one milligram once weekly via subcutaneous injection, and empagliflozin (Jardiance®), 25 mg daily, orally. We additionally consider background therapy alone, consisting of metformin (with or without sulfonylureas). Greater emphasis is placed on the common comparator of background therapy alone in scenario analyses, as some of these scenarios focus on comparisons across modeled results and trial outcomes versus background therapy alone.

## E2. Model Inputs and Assumptions

Key model inputs and assumptions are listed in the main text in [section 4.2](#).

### Model Inputs

#### *Clinical Inputs*

Baseline clinical inputs came from the individual patients in the target population, derived from NHANES dataset.

We used the point estimates and 95% credible ranges from the random effects model output of the network meta-analysis described above as the treatment effects in the model for the following outcomes: decrease in HbA1c level, decrease in weight, decrease in systolic blood pressure (SBP), and decrease in low-density lipids (LDL). These values can be found in the section reporting NMA output.

#### Response to Treatment

Clinical inputs regarding the efficacy of tirzepatide, injectable semaglutide, and empagliflozin as compared to placebo on intermediate outcomes such as changes in HbA1c, lipid levels, blood pressure, and body weight were derived from the NMA described above. The treatment effect was assumed to take effect after the first model cycle only, at which point it would be maintained while the patient was on treatment. Ongoing changes in weight and HbA1c were modeled using published equations for those measures in treated diabetic patients.<sup>61</sup>

We applied hazard ratios to estimated outcomes, including major adverse cardiac events, congestive heart failure, and nephropathy (Table E.2.). Hazard ratios were derived from clinical outcome trials SUSTAIN-6 for injectable semaglutide and from EMPA-REG OUTCOME for empagliflozin.<sup>7,35</sup> They were applied by multiplying the UKPDS predicted probability of the event occurring by the HR in each model cycle. No adjustment was made to tirzepatide in the base case for congestive heart failure and nephropathy, reflected by setting the hazard ratios equal to one. Tirzepatide's hazard ratio for major adverse cardiac events was set equal to the risk reduction observed in SURPASS-4, which is also an equivalent point estimate to semaglutide's SUSTAIN-6. The decision to only modify one group of the risk equation estimates for tirzepatide in the base case was based primarily on two factors: a lack of available cardiovascular and renal outcome data to reference and the lack of reliable proxy data due to tirzepatide's novel dual mechanism of action. We also tested a scenario where all hazard ratios for tirzepatide were neutralized (set equal to 1).

**Table E.2. Hazard Ratios Applied in Base-Case Analysis**

| Regimen                            | Hazard Ratio | Source                          |
|------------------------------------|--------------|---------------------------------|
| <b>Composite MACE HR</b>           |              |                                 |
| Tirzepatide HR vs. Background Tx   | 0.74         | SURPASS-4 <sup>34</sup>         |
| Semaglutide HR vs. Background Tx   | 0.74         | SUSTAIN-6. <sup>7</sup>         |
| Empagliflozin HR vs. Background Tx | 0.86         | EMPA-REG -OUTCOME <sup>35</sup> |
| <b>Congestive Heart Failure HR</b> |              |                                 |
| Tirzepatide HR vs. Background Tx   | 1.00         | Assumption                      |
| Semaglutide HR vs. Background Tx   | 1.11         | SUSTAIN-6. <sup>7</sup>         |
| Empagliflozin HR vs. Background Tx | 0.65         | EMPA-REG -OUTCOME <sup>35</sup> |
| <b>Nephropathy HR</b>              |              |                                 |
| Tirzepatide HR vs. Background Tx   | 1.00         | Assumption                      |
| Semaglutide HR vs. Background Tx   | 0.64         | SUSTAIN-6. <sup>7</sup>         |
| Empagliflozin HR vs. Background Tx | 0.61         | EMPA-REG -OUTCOME <sup>35</sup> |

HR: hazard ratio, MACE: major adverse cardiovascular event, Tx: treatment

### Treatment Discontinuation

The only therapy with extension trial data beyond initial clinical trials was empagliflozin (EMPA-REG EXTEND), with discontinuation data for patients for 52 weeks assuming they continued the therapy for at least the initial 24 weeks. We derived the probability of discontinuation during the first year after the initial trial period (9.1% per year) from patients who discontinued for any reason; the rationale for choosing discontinuation for any reason was to accurately reflect the number of patients no longer benefiting from the drug regardless of reason. This rate was applied to all included active therapies pending long term trial data availability. Discontinuation of background therapy was derived from the placebo arms of trials for the three active comparators: SURPASS-1, EMPA-REG EXTEND, and SUSTAIN 2.

### Addition of Insulin Therapy

Patients whose HbA1c levels reach 8.5% or above (with a range from 8.0 to 9.0% used in scenario analyses) were assumed to add insulin therapy while continuing on active therapy. Patients were assumed to continue both insulin and their active treatment for the remainder of the model time horizon. Patients being modeled on background therapy alone were assumed to discontinue their background therapy when insulin therapy started. The choice for insulin to be added on top of active therapy was made for several reasons: it reflects the same treatments for GLP-1 and SGLT-2 therapies in the 2019 ICER report; it reflects what we believe would occur in clinical practice; and it allows us to be able to evaluate all comparators head-to-head as opposed to evaluating differences in different medication treatment pathways. Insulin treatment costs were modeled using mean doses from a literature review, applied to unit costs similar to the model comparators.<sup>61</sup> Clinical characteristics for patients on insulin were modeled using the UKPDS-OM2 and Willis equations.<sup>10,61</sup>

### Diabetes-related Complications

We modeled diabetes-related complications and mortality based on risk equations from the UKPDS-OM2 risk engine.<sup>10</sup> The UKPDS-OM2 risk equations are widely used in diabetes simulation models, and have been shown to accurately predict results for the population in which it was developed as well as other diabetes populations.<sup>10,119,120</sup> The UKPDS-OM2 complications (13 risk equations) include CHF, ischemic heart disease (IHD), first MI for females, first MI for males, subsequent MI, first stroke, subsequent stroke, blindness, foot ulcer, first amputation without prior ulcer, first amputation with prior ulcer, subsequent amputation, and ESRD.<sup>10</sup> In the microsimulation, patients were able to experience multiple and concurrent complications during each modeled year. The UKPDS-OM2 mortality risk equations predict that previous T2DM-related complications (except foot ulcer and blindness) increase the probability of death. The four mutually exclusive mortality risk equations were death without history of complication(s), death in the year of a clinical event, death in subsequent year of prior event(s), and death with history of clinical event(s).<sup>10</sup>

The effect of included add-on therapies on intermediate outcomes, including several of the time-varying risk factors mentioned above, were applied to the patients and the treatment effect was assumed to persist until patient death or therapy discontinuation. We estimated the effect of included add-on therapies on cardiovascular and renal outcomes in the base case via the reductions in HbA1c, weight, SBP, and LDL, allowing changes in intermediate outcomes to be associated with longer-term outcomes. We also applied hazard ratios from the placebo-controlled cardiovascular outcomes trials for the add-on therapies.

### Treatment Discontinuation and Insulin Uptake

We applied a single discontinuation rate due to any cause from the empagliflozin extension trial EMPA-REG EXTEND to all therapies, as long-term discontinuation data was not available for

injectable semaglutide or tirzepatide, at the end of cycle 1. Patients discontinuing their primary modeled treatment were assumed to transition to insulin therapy. This choice was made to facilitate head-to-head comparator evaluations as opposed to evaluating differences in multiple potential treatment pathways. All patients who discontinued used insulin in addition to background treatment for the remainder of the model time horizon. After cycle 1, we also assumed that patients initiated insulin (in addition to their add-on treatment) if their HbA1c reached 8.5 or above. Insulin treatment costs were based on a multivariate prediction model for estimating long-term HbA1c change, weight change, and hypoglycemic events associated with insulin rescue medication.<sup>61</sup> After cycle 1, clinical characteristics for patients pre- and post-insulin were modeled using the equations for HbA1c and weight change,<sup>61</sup> which then influenced the UKPDS-OM2 complication risk equations for those patients. The hypoglycemia equations from the Willis et al. prediction model were not used due to their substantial uncertainty.

### Hypoglycemia

Mild, moderate, and severe hypoglycemia were modeled in cycles 2+ based on the previous UKPDS-OM2 adaptation from Laiteerapong et al.<sup>52</sup> Patients not yet receiving insulin were assumed to have a 5% probability for a severe hypoglycemic event and a 33% probability for a mild or moderate event each year. Patients receiving insulin were assumed to have a 21% probability of a severe hypoglycemic event and a 52% probability of a mild or moderate hypoglycemic event each year. Patients were assumed to have no more than one mild or moderate hypoglycemic event and one severe hypoglycemic event per year but could have multiple hypoglycemic events during their lifetime.

### Atrial Fibrillation and Peripheral Artery Disease

The UKPDS-OM2 equations have coefficients for atrial fibrillation and peripheral vascular (artery) disease but the NHANES patient dataset did not provide this information. Therefore, we utilized age-based cumulative incidence estimates from the US population<sup>121,122</sup> and (for atrial fibrillation) relative risk estimates based on patients' HbA1c,<sup>123</sup> to simulate these patient characteristics prior to each microsimulation. Peripheral vascular disease and atrial fibrillation prevalence were modeled independent of existing patient characteristics.

## Mortality

The UKPDS-OM2 risk equations predict mortality using four mutually exclusive equations that are stratified based on the person's prior T2DM event history and whether the mortality event is related to a cardiovascular event.<sup>10</sup>

## Utilities

We used consistent health state utility values across treatments evaluated in the model. Separate utilities were used for the year in which a complication occurred and for patient history of each complication, where applicable. Health state utilities were derived from publicly available literature and/or manufacturer-submitted data and applied to the modeled events. We used regression-based estimates for T2DM complications primarily from Shao et al.<sup>124,125</sup> In Shao et al., the Health Utilities Index Mark 3 (HUI-3) was used to measure health utility in a sample of 8,713 patients from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of high cardiovascular disease risk T2DM patients.<sup>125</sup> Lastly, we additively modeled an annual disutility for daily injection of insulin (for patients who progressed) based on Boye et al., who used standard gamble interviews of T2DM patients in Scotland to estimate the utility values for injection-related attributes.<sup>126</sup>

**Table E.3. Utility Values Used in Model**

| Health Event or History            | (Dis)Utility | Source                         |
|------------------------------------|--------------|--------------------------------|
| Baseline T2DM Utility              | 0.800        | Shao et al. <sup>125</sup>     |
| <b>Macrovascular Complications</b> |              |                                |
| Congestive Heart Failure Event     | -0.089       | Shao et al. <sup>125</sup>     |
| Congestive Heart Failure History   | -0.041       | Shao et al. <sup>125</sup>     |
| Ischemic Heart Disease History     | -0.016       | Shao et al. <sup>125</sup>     |
| Myocardial Infarction Event        | -0.042       | Shao et al. <sup>125</sup>     |
| Myocardial Infarction History      | -0.011       | Shao et al. <sup>125</sup>     |
| Stroke Event                       | -0.204       | Shao et al. <sup>125</sup>     |
| Stroke History                     | -0.101       | Shao et al. <sup>125</sup>     |
| <b>Microvascular Complications</b> |              |                                |
| Blindness History                  | -0.057       | Shao et al. <sup>125</sup>     |
| Foot Ulcer Event                   | -0.024       | Sullivan et al. <sup>127</sup> |
| Amputation Event                   | -0.051       | Sullivan et al. <sup>127</sup> |
| Renal Disease History              | -0.024       | Shao et al. <sup>125</sup>     |
| <b>Hypoglycemia</b>                |              |                                |
| Hypoglycemia Event                 | -0.036       | Shao et al. <sup>125</sup>     |
| Hypoglycemia History               | -0.033       | Shao et al. <sup>125</sup>     |

|  |        |                            |
|--|--------|----------------------------|
| <b>Demographic characteristics</b>     |        |                            |
| Age at Diagnosis (per year $\geq 52$ ) | -0.002 | Shao et al. <sup>125</sup> |
| Female                                 | -0.043 | Shao et al. <sup>125</sup> |
| Race (ref = Black)                     |        |                            |
| Hispanic                               | -0.045 | Shao et al. <sup>125</sup> |
| Others                                 | -0.010 | Shao et al. <sup>125</sup> |
| White                                  | -0.019 | Shao et al. <sup>125</sup> |
| Current Smoker                         | -0.054 | Shao et al. <sup>125</sup> |
| BMI (per unit $\geq 32$ )              | -0.007 | Shao et al. <sup>125</sup> |
| Diabetes Duration (per year)           | -0.005 | Shao et al. <sup>125</sup> |
| <b>Injection-related Disutility</b>    |        |                            |
| Annual Disutility for Tx Injection     | -0.054 | Boye et al. <sup>126</sup> |

BMI: body mass index, Tx: treatment

## ***Economic Inputs***

### ***Drug Acquisition Costs***

Because tirzepatide is not approved by the FDA, the drug price is not yet available. Based on the [ICER Reference Case](#), we investigated calculation of a placeholder price based on the average of all available once-weekly injectable GLP-1 RAs. However, we uncovered that discounted pricing for once-weekly injectable Bydureon BCise® (exenatide extended-release) is approximately three times that of Ozempic® (semaglutide), suggesting it may be an unsuitable proxy to inform tirzepatide placeholder pricing. Given this, we used the price of Ozempic® (semaglutide) as a placeholder price for tirzepatide and calculated the threshold prices at the standard cost-effectiveness thresholds: \$50,000 through \$200,000 per QALY; we did not calculate cost-effectiveness thresholds in terms of equal value of life years (evLYs) gained given no average increased survival when comparing tirzepatide with injectable semaglutide. We applied the semaglutide drug discount rate to obtain net pricing estimates for tirzepatide.

### ***Health Care Utilization Costs***

**Table E.4. Cost per T2DM-Related Complication and per Hypoglycemic Event**

| Incremental Cost in the Year of Event/Diagnosis (per event) | Estimate (2021 USD)* | Source             |
|---|----------------------|--------------------|
| <b>Year of Event (per event)</b>                            |                      | Yang <sup>64</sup> |
| Congestive Heart Failure                                    | \$34,898             | Yang <sup>64</sup> |
| Ischemic Heart Disease                                      | \$9,962              | Yang <sup>64</sup> |

|   |           |                            |
|---|-----------|----------------------------|
| Myocardial Infarction                     | \$50,612  | Yang <sup>64</sup>         |
| Stroke                                    | \$26,597  | Yang <sup>64</sup>         |
| Foot Ulcer                                | \$2,691   | Ward <sup>63</sup>         |
| Amputation                                | \$11,330  | Ward <sup>63</sup>         |
| Hypoglycemia                              |           |                            |
| Requiring Hospitalization                 | \$8,563   | Yang <sup>64</sup>         |
| Requiring ER Visit                        | \$1,643   | Yang <sup>64</sup>         |
| Requiring Glucagon Injection              | \$221     | Yang <sup>64</sup>         |
| <b>History of Complication (per year)</b> |           |                            |
| Congestive Heart Failure                  | \$7,899   | Yang <sup>64</sup>         |
| Ischemic Heart Disease                    | \$2,386   | Ward <sup>63</sup>         |
| Myocardial Infarction                     | \$9,587   | Yang <sup>64</sup>         |
| Stroke                                    | \$5,289   | Yang <sup>64</sup>         |
| Blindness                                 | \$14,534  | Yang <sup>64</sup>         |
| Renal Disease                             | \$105,394 | Yang <sup>64</sup>         |
| <b>Health Care Use Costs</b>              |           |                            |
| Outpatient Visit: Non-Insulin             | \$584     | Laiteerapong <sup>52</sup> |
| Outpatient Visit: Insulin                 | \$639     | Laiteerapong <sup>52</sup> |

ER: emergency room, ESRD: end-stage renal disease, USD: United States dollars

\*Costs inflated to USD 2021 using US government Bureau of Labor Statistics Consumer Price Index

### Adverse Event Costs and Disutilities

No serious treatment-related adverse events occurring in greater than 5% of the patient population were observed. Adverse events occurring under that rate generally have minimal effect on the model output and therefore were not included in the model. Overall TRAEs and other reasons for discontinuing treatment were addressed in a global fashion through cardiac events, treatment discontinuation, etc. We also included an annual disutility due to daily insulin injections in the utility section.

### Productivity Costs

We sought to include a modified societal perspective in this analysis. However, we found a paucity of data to inform such modeling. Instead, we performed calculations utilizing the model's incremental health gains (QALYs gained) and a measure of the productivity impact of T2DM to approximate the modified societal perspective results. We adjusted Dall et al.'s estimate of the productivity costs of T2DM from 2017 to 2021 US Dollars using the health care component of the Consumer Price Index, resulting in annual productivity costs of \$5842.<sup>128</sup> That annual estimate was assumed to be the potential savings associated with each incremental QALY for an intervention versus a comparator. We multiplied the annual productivity estimate times the incremental QALYs to estimate the assumed societal cost savings and combined these assumed productivity-based

savings with the total incremental payer perspective costs in order to calculate cost-effectiveness ratios for the modified societal perspective.

## E3. Results

### Disaggregated and Undiscounted Base-Case Results

To estimate the overarching lifetime costs and benefits of each active therapy and background treatment alone, the model calculated the average disaggregated values, including the percent of patients experiencing disease-related events, add-on agent costs, background treatment costs, and event-related health care costs. The averages of each of those values, along with 95% credible ranges, are presented in Table E3.1. for each active therapy and background treatment alone. We also calculated cost and outcome variables without discounting, presented in Table E3.2. EvLYs and evLYs gained were not reported given no average increased survival when comparing tirzepatide with injectable semaglutide.

**Table E3.1. Disaggregated Results of the Base-Case Model**

|               | Tirzepatide |                         | Semaglutide |                         | Empagliflozin |                         | Background Tx |                         |
|---------------|-------------|-------------------------|-------------|-------------------------|---------------|-------------------------|---------------|-------------------------|
|               | Mean        | 95% CR                  | Mean        | 95% CR                  | Mean          | 95% CR                  | Mean          | 95% CR                  |
| <b>Costs</b>  |             |                         |             |                         |               |                         |               |                         |
| Total Cost    | \$306,000   | (\$275,000 - \$339,000) | \$309,000   | (\$280,000 - \$339,000) | \$276,000     | (\$248,000 - \$305,000) | \$262,000     | (\$234,000 - \$291,000) |
| Add-on Agent  | \$40,500    | (\$38,200 - \$42,900)   | \$41,200    | (\$38,800 - \$43,500)   | \$12,000      | (\$11,300 - \$12,700)   | \$0           | (\$0 - \$0)             |
| Background Tx | \$4,200     | (\$3,900 - \$4,400)     | \$4,200     | (\$4,000 - \$4,400)     | \$4,100       | (\$3,900 - \$4,300)     | \$3,700       | (\$3,500 - \$3,900)     |
| Insulin       | \$8,200     | (\$7,100 - \$9,300)     | \$10,400    | (\$9,300 - \$11,600)    | \$13,300      | (\$12,100 - \$14,600)   | \$14,500      | (\$13,300 - \$15,800)   |
| Health Care   | \$5,600     | (\$5,300 - \$5,900)     | \$5,800     | (\$5,500 - \$6,000)     | \$5,600       | (\$5,300 - \$5,800)     | \$5,100       | (\$4,900 - \$5,400)     |
| CHF           | \$18,300    | (\$15,500 - \$21,400)   | \$21,500    | (\$18,600 - \$24,800)   | \$16,400      | (\$13,700 - \$19,200)   | \$18,100      | (\$15,200 - \$21,100)   |
| IHD           | \$3,300     | (\$2,600 - \$4,000)     | \$3,400     | (\$2,800 - \$4,100)     | \$3,300       | (\$2,600 - \$4,000)     | \$2,900       | (\$2,300 - \$3,600)     |
| MI            | \$22,400    | (\$18,900 - \$26,000)   | \$25,000    | (\$21,200 - \$29,000)   | \$27,200      | (\$23,500 - \$31,300)   | \$26,000      | (\$22,000 - \$30,000)   |
| Stroke        | \$10,100    | (\$8,100 - \$12,400)    | \$11,900    | (\$9,600 - \$14,400)    | \$13,000      | (\$10,700 - \$15,600)   | \$12,500      | (\$10,300 - \$14,800)   |
| Blindness     | \$4,600     | (\$2,600 - \$7,000)     | \$5,400     | (\$3,300 - \$7,800)     | \$5,400       | (\$3,300 - \$7,900)     | \$5,100       | (\$3,100 - \$7,500)     |
| Foot Ulcer    | \$300       | (\$200 - \$500)         | \$400       | (\$300 - \$500)         | \$400         | (\$300 - \$600)         | \$400         | (\$300 - \$600)         |
| Amputation    | \$2,500     | (\$1,800 - \$3,300)     | \$3,000     | (\$2,300 - \$4,000)     | \$3,300       | (\$2,500 - \$4,200)     | \$3,000       | (\$2,300 - \$3,900)     |
| Renal Disease | \$175,000   | (\$147,000 - \$204,000) | \$164,000   | (\$139,000 - \$191,000) | \$158,000     | (\$134,000 - \$184,000) | \$157,000     | (\$133,000 - \$184,000) |



|                        |          |                       |          |                       |          |                       |          |                       |
|------------------------|----------|-----------------------|----------|-----------------------|----------|-----------------------|----------|-----------------------|
| Hypoglycemia           | \$11,000 | (\$10,300 - \$12,600) | \$12,500 | (\$11,400 - \$13,700) | \$13,600 | (\$12,500 - \$14,900) | \$13,500 | (\$12,400 - \$14,800) |
| <b>Health Outcomes</b> |          |                       |          |                       |          |                       |          |                       |
| QALYs                  | 4.90     | (4.68 - 5.12)         | 4.85     | (4.64 - 5.05)         | 4.60     | (4.40 - 4.79)         | 4.13     | (3.95 - 4.33)         |
| Life Years             | 9.36     | (8.91 - 9.83)         | 9.53     | (9.08 - 9.97)         | 9.17     | (8.73 - 9.61)         | 8.34     | (7.93 - 8.77)         |
| <b>Complications</b>   |          |                       |          |                       |          |                       |          |                       |
| CHF                    | 29.9%    | (25.6% - 34.4%)       | 34.8%    | (30.5% - 39.3%)       | 27.2%    | (23.0% - 31.5%)       | 30.1%    | (25.6% - 34.6%)       |
| IHD                    | 14.5%    | (11.4% - 18.1%)       | 15.3%    | (11.9% - 18.9%)       | 14.6%    | (11.1% - 18.1%)       | 13.3%    | (10.1% - 16.5%)       |
| 1st MI                 | 27.3%    | (23.5% - 31.3%)       | 29.2%    | (25.1% - 33.1%)       | 32.4%    | (28.4% - 36.7%)       | 34.0%    | (29.7% - 38.2%)       |
| Subs. MI               | 3.7%     | (2.1% - 5.9%)         | 4.4%     | (2.3% - 6.7%)         | 5.4%     | (3.1% - 8.0%)         | 4.8%     | (2.8% - 7.2%)         |
| 1st Stroke             | 23.3%    | (19.4% - 27.4%)       | 25.7%    | (21.4% - 29.7%)       | 28.8%    | (24.5% - 33.3%)       | 30.0%    | (25.8% - 34.4%)       |
| Subs. Stroke           | 9.6%     | (4.7% - 17.3%)        | 12.7%    | (6.2% - 22.5%)        | 13.7%    | (7.2% - 23.3%)        | 11.3%    | (5.9% - 19.1%)        |
| Blindness              | 8.6%     | (5.9% - 11.6%)        | 10.0%    | (7.0% - 12.9%)        | 10.2%    | (7.2% - 13.2%)        | 9.9%     | (7.0% - 12.9%)        |
| Foot Ulcer             | 18.2%    | (11.1% - 28.4%)       | 23.0%    | (14.5% - 34.6%)       | 24.7%    | (15.8% - 36.7%)       | 22.6%    | (14.5% - 33.3%)       |
| 1st Amp, No Ulcer      | 16.1%    | (12.7% - 19.9%)       | 18.1%    | (14.5% - 22.0%)       | 19.0%    | (15.2% - 22.7%)       | 17.8%    | (14.2% - 21.7%)       |
| 1st Amp, Ulcer         | 3.8%     | (2.1% - 5.7%)         | 4.4%     | (2.6% - 6.5%)         | 4.6%     | (2.6% - 6.7%)         | 4.3%     | (2.3% - 6.5%)         |
| Subs. Amp              | 17.2%    | (8.5% - 30.2%)        | 23.0%    | (12.1% - 39.0%)       | 24.2%    | (12.9% - 40.3%)       | 19.1%    | (10.1% - 31.8%)       |
| Renal Disease          | 15.9%    | (12.7% - 19.1%)       | 12.8%    | (9.8% - 15.8%)        | 12.5%    | (9.3% - 15.8%)        | 14.5%    | (11.4% - 17.8%)       |

CHF: congestive heart failure, IHD: ischemic heart disease, MI: myocardial infarction, QALY: quality-adjusted life year, Tx: treatment

**Table E3.2 Undiscounted Results from Base Case**

|                           | Tirzepatide |                         | Semaglutide |                         | Empagliflozin |                         | Background Tx |                         |
|---------------------------|-------------|-------------------------|-------------|-------------------------|---------------|-------------------------|---------------|-------------------------|
|                           | Mean        | 95% CR                  | Mean        | 95% CR                  | Mean          | 95% CR                  | Mean          | 95% CR                  |
| <b>Undiscounted Costs</b> |             |                         |             |                         |               |                         |               |                         |
| Total Cost                | \$408,000   | (\$362,000 - \$456,000) | \$413,000   | (\$370,000 - \$458,000) | \$366,000     | (\$324,000 - \$407,000) | \$341,000     | (\$300,000 - \$383,000) |
| Add-on Agent              | \$52,600    | (\$49,100 - \$56,400)   | \$53,700    | (\$50,100 - \$57,300)   | \$15,400      | (\$14,400 - \$16,500)   | \$0           | (\$0 - \$0)             |
| Background Tx             | \$5,400     | (\$5,100 - \$5,800)     | \$5,500     | (\$5,200 - \$5,900)     | \$5,300       | (\$5,000 - \$5,600)     | \$4,700       | (\$4,400 - \$5,000)     |
| Insulin                   | \$12,600    | (\$10,900 - \$14,400)   | \$15,900    | (\$14,000 - \$18,000)   | \$19,300      | (\$17,300 - \$21,400)   | \$20,200      | (\$18,200 - \$22,300)   |
| Health Care               | \$7,400     | (\$6,900 - \$7,800)     | \$7,600     | (\$7,100 - \$8,000)     | \$7,300       | (\$6,900 - \$7,700)     | \$6,500       | (\$6,100 - \$7,000)     |
| CHF                       | \$26,000    | (\$21,900 - \$30,500)   | \$30,500    | (\$26,100 - \$35,300)   | \$23,100      | (\$19,200 - \$27,200)   | \$24,600      | (\$20,600 - \$28,800)   |
| IHD                       | \$4,500     | (\$3,500 - \$5,500)     | \$4,800     | (\$3,700 - \$5,800)     | \$4,500       | (\$3,500 - \$5,500)     | \$3,800       | (\$3,000 - \$4,800)     |

|                                       |           |                         |           |                         |           |                         |           |                         |
|---------------------------------------|-----------|-------------------------|-----------|-------------------------|-----------|-------------------------|-----------|-------------------------|
| MI                                    | \$30,900  | (\$25,900 - \$36,100)   | \$34,800  | (\$29,200 - \$40,800)   | \$37,300  | (\$31,700 - \$43,200)   | \$34,300  | (\$29,200 - \$39,700)   |
| Stroke                                | \$14,400  | (\$11,500 - \$18,000)   | \$17,100  | (\$13,700 - \$21,400)   | \$18,500  | (\$15,000 - \$22,600)   | \$17,000  | (\$14,000 - \$20,500)   |
| Blindness                             | \$7,500   | (\$4,300 - \$11,500)    | \$9,000   | (\$5,400 - \$13,100)    | \$8,900   | (\$5,300 - \$13,100)    | \$8,100   | (\$4,800 - \$11,900)    |
| Foot Ulcer                            | \$490     | (\$300 - \$800)         | \$600     | (\$400 - \$900)         | \$700     | (\$400 - \$1,000)       | \$600     | (\$400 - \$900)         |
| Amputation                            | \$4,200   | (\$3,000 - \$5,900)     | \$5,200   | (\$3,700 - \$7,100)     | \$5,400   | (\$3,900 - \$7,400)     | \$4,700   | (\$3,400 - \$6,300)     |
| Renal Disease                         | \$226,000 | (\$186,000 - \$269,000) | \$211,000 | (\$175,000 - \$250,000) | \$202,000 | (\$166,000 - \$238,700) | \$198,000 | (\$164,000 - \$236,000) |
| Hypoglycemia                          | \$15,900  | (\$14,200 - \$17,600)   | \$17,400  | (\$15,700 - \$19,200)   | \$18,600  | (\$16,900 - \$20,500)   | \$17,900  | (\$16,200 - \$19,800)   |
| <b>Survival Time-related Outcomes</b> |           |                         |           |                         |           |                         |           |                         |
| Undiscounted Time on Tx (Years)       | 11.33     | (10.60 - 12.13)         | 11.56     | (10.78 - 12.33)         | 11.02     | (10.28 - 11.77)         | NA        | NA                      |
| Undiscounted Life Years               | 12.20     | (11.52 - 12.95)         | 12.45     | (11.74 - 13.15)         | 11.87     | (11.19 - 12.57)         | 10.59     | (9.96 - 11.25)          |

CHF: congestive heart failure, IHD: ischemic heart disease, MI: myocardial infarction, QALY: quality-adjusted life year, Tx: treatment

## E4. Sensitivity Analyses

Additionally, we ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input. In order to efficiently operationalize the one-way sensitivity analysis within the framework of the patient-level microsimulation, we fixed the parameter values for all non-patient-level inputs and then performed 10 UKPDS equation simulations for each of 387 NHANES patients for each parameter's low and high value, for each treatment, in order to produce an estimate of uncertainty for each high and low value of each parameter. Therefore, each one-way sensitivity analysis output value represents the average impact over the 10 simulations of the 387 individual patient simulations. Individual one-way sensitivity analyses were performed for incremental costs and incremental QALYs in order to isolate the impact of the inputs on those individual outcomes. The results of these one-way sensitivity analyses are presented as tornado diagrams.

Here we present comparisons between tirzepatide and empagliflozin, and tirzepatide and background therapy alone. The tornado diagram for incremental costs was truncated to include inputs with at least a \$500 difference between the high and low value. The tornado diagram for incremental QALYs was truncated to include inputs with more than a 0.01 QALY difference between the high and low value.

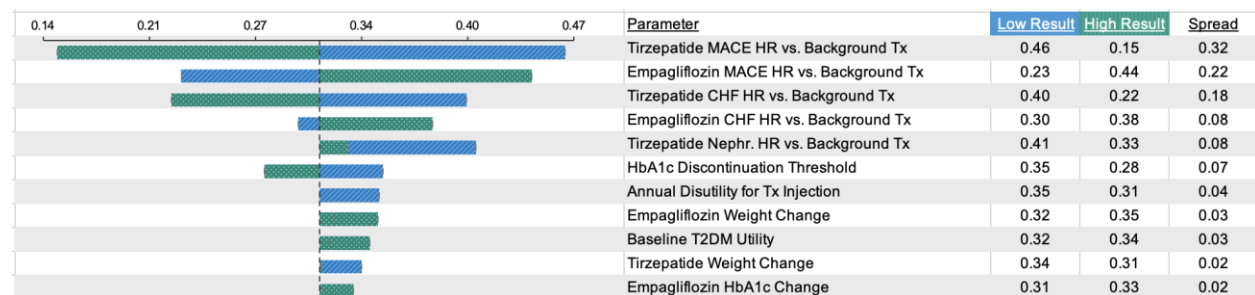
**Figure E.1. Incremental Costs Tornado Diagram (Tirzepatide vs. Empagliflozin)\***



CHF: congestive heart failure, HbA1c: Hemoglobin A1c/glycosylated hemoglobin, HR: hazard ratio, MACE: major adverse cardiovascular event, Tx: treatment

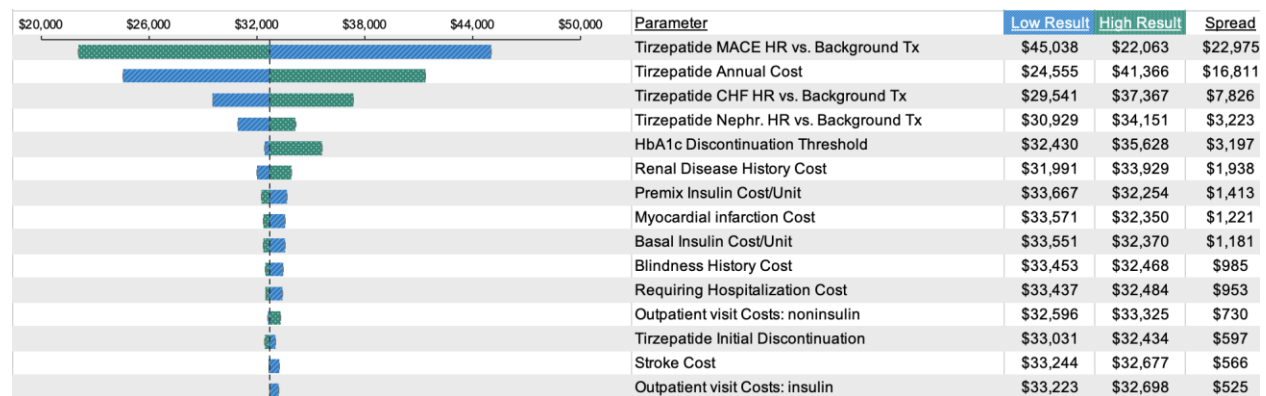
\*Using a placeholder price for tirzepatide

**Figure E.2. Incremental QALYs Tornado Diagram (Tirzepatide vs. Empagliflozin)**



CHF: congestive heart failure, HbA1c: Hemoglobin A1c/glycosylated hemoglobin, HR: hazard ratio, MACE: major adverse cardiovascular event, QALY: quality-adjusted life-year, Tx: treatment

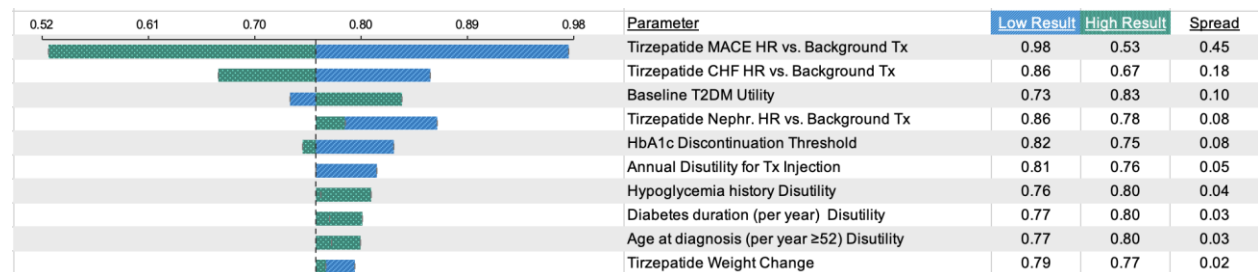
**Figure E3. Incremental Costs Tornado Diagram (Tirzepatide vs. Background Therapy Alone)\***



CHF: congestive heart failure, HR: hazard ratio, MACE: major adverse cardiovascular event, Tx: treatment

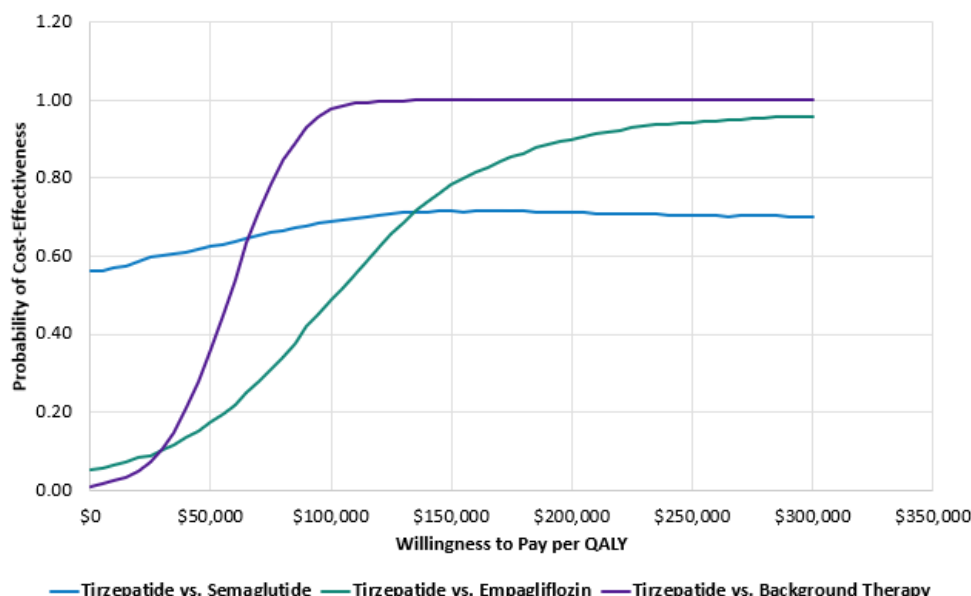
\*Using a placeholder price for tirzepatide

**Figure E4. Incremental QALYs Tornado Diagram (Tirzepatide vs. Background Therapy Alone)**



HbA1c: Hemoglobin A1c/glycosylated hemoglobin, HR: hazard ratio, MACE: major adverse cardiovascular event, QALY: quality-adjusted life-year, Tx: treatment

**Figure E.5. Base-Case Cost-Effectiveness Acceptability Curves for Tirzepatide vs. Semaglutide, Empagliflozin, and Background Therapy Alone Using Placeholder Price**



## E5. Scenario Analyses

We ran the following separate scenario analyses to understand the impact of some of our assumptions within the model when comparing tirzepatide plus background therapy to background therapy alone: we shortened the time horizon to 10 years; we set tirzepatide's CV and renal event adjustment equal to that of semaglutide; we gave no adjustment to tirzepatide's CV and renal event estimations; we set the insulin initiation threshold due to advanced HbA1c levels to both 8% and to 9% as opposed to the base case 8.5%; we ran the model without applying risk factor progression for HbA1c and weight; and we removed utility benefit for BMI change. For each of these scenarios, the results presented represent the mean and 95% credible range from probabilistic sensitivity analyses comprised of 500 simulations of each of the 387 people from NHANES with T2DM.

**Table E5. Scenario Analyses Incremental Results for Tirzepatide Added to Background Therapy vs. Background Therapy Alone, mean (95% credible range)\***

| Scenario Description   | Incremental Cost per QALY Gained | Incremental Cost per Life Year Gained |
|--|----------------------------------|---------------------------------------|
| Base-Case Scenario   | \$58,000                         | \$44,000                              |
|  | (\$10,900 to \$99,100)           | (\$10,400 to \$82,500)                |
| 10-year Time Horizon   | \$49,000                         | \$59,000                              |
|  | (-\$10,300 to \$101,500)         | (-\$54,800 to \$223,500)              |
| Tirzepatide CV and Renal Benefit with No Hazard Ratio Adjustment | \$58,000                         | \$57,000                              |
|  | (-\$13,000 to \$115,000)         | (-\$20,000 to \$278,500)              |
| Insulin When HbA1c=8%  | \$55,000                         | \$42,000                              |
|  | (\$12,000 to \$94,300)           | (\$11,100 to \$77,200)                |
| Insulin When HbA1c=9%  | \$64,000                         | \$46,000                              |
|  | (\$19,400 to \$111,700)          | (\$15,400 to \$87,400)                |
| No Willis Equations (no risk factor progression assumptions)     | \$60,000                         | \$47,000                              |
|  | (\$3,500 to \$106,000)           | (\$3,900 to \$106,200)                |
| No disutility due to BMI   | \$62,000                         | \$42,000                              |
|  | (\$13,200 to \$109,100)          | (\$10,100 to \$82,900)                |

BMI: body mass index, CV: cardiovascular, HbA1c: hemoglobin levels, QALY: quality-adjusted life-year

\*Using a placeholder price for tirzepatide

#### *Modified Societal Perspective Scenario Estimation, Using Missing Data Assumptions*

We used a placeholder price for tirzepatide and assumed that the incremental QALYs gained by tirzepatide were associated with avoiding productivity losses associated with T2DM. Our calculation of the estimated value of tirzepatide compared to background therapy alone under this modified societal perspective using missing data assumptions, resulted in incremental cost-effectiveness ratios of \$52,600 per QALY gained and \$39,200 per life year gained.

## **E6. Model Validation**

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and in supplemental materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

We also performed external validation by running the model for 2- and 3-year outcomes without hazard ratio adjustments and presented the results next to available cardiovascular outcome trial data (Table E6). We shortened the time horizon to more closely resemble the conditions in the

trials and to provide insight into clinical event rates and risk factor progression against the base-case lifetime model.

**Table E6. 2-year and 3-year Time Horizon Model Event Estimates Compared to Cardiovascular Outcome Trial Output**

|                     |   | Semaglutide |              | Placebo/Background Only |              | Empagliflozin      |              | Placebo/Background Only |              |
|---------------------|---|-------------|--------------|-------------------------|--------------|--------------------|--------------|-------------------------|--------------|
| Trial Outcomes      | Model Outcome Used                        | SUSTAIN-6   | 2-year Model | SUSTAIN-6               | 2-year Model | EMPA-REG - OUTCOME | 3-year Model | EMPA-REG - OUTCOME      | 3-year Model |
| Composite Outcome   | Summed MACE w/o double counting CV death  | 6.6%        | 8.1%         | 8.9%                    | 12.4%        | 10.5%              | 14.9%        | 12.1%                   | 18.0%        |
| All-Cause Mortality | Ratio of Undiscounted LYs to Time Horizon | 3.8%        | 3.0%         | 3.6%                    | 3.5%         | 5.7%               | 6.0%         | 8.3%                    | 6.7%         |
| CV Mortality        | CV Death (UKPDS Eq)                       | 2.7%        | 1.5%         | 2.8%                    | 2.9%         | 3.7%               | 3.1%         | 5.9%                    | 4.0%         |

## Prior Economic Models

In our review of the literature, we found no cost-effectiveness model that compared tirzepatide to other T2DM treatment strategies. Our focus in this section is therefore to review and contrast the methodologies used in the modeling of T2DM treatment strategies. The numerous available strategies and pathways available for the treatment of T2DM have led to the development and publication of several cost-effectiveness analyses and modeling exercises in the past few decades, many of which highlight the comparators used in this analysis.<sup>54,55,120,129,130</sup> Such analyses include both cohort and microsimulation models. For the purposes of this report, we have limited the comparison to other published microsimulation models, specifically the following: 1) the UKPDS OM2 (a model predicting health outcomes in T2DM)<sup>10</sup>, 2) a microsimulation cost utility model by Laiteerapong et al.<sup>52</sup>, 3) the model published in ICER's 2019 report of oral semaglutide on T2DM outcomes, of which this model is an adaptation<sup>39,53</sup>, and 4) models published since the previous ICER T2DM report using the IQVIA Core Diabetes Model assessing our included comparators.<sup>131,132</sup>

The UKPDS-OM2 is an update of the original UKPDS-Outcomes Model 1 (OM1), also a patient simulation model that predicts health outcomes of patients with T2DM. The UKPDS-OM2 re-estimated the original seven risk equations in the UKPDS-OM1 over a longer time-horizon plus additional risk equations for other complications such as diabetic ulcer. Additionally, it also included new risk equations for all-cause mortality in T2DM patients. Our model applied the updated UKPDS-OM2 risk equations (developed for the UK population) to a US-specific population

that was derived from 2013-2014, 2015-2016, and 2017-2018 NHANES survey data on 387 patients that fit the baseline characteristics of patients with uncontrolled T2DM taking metformin but not another type of add-on diabetes therapy. Our model also assumed risk factor progression by applying published risk factor progression equations for weight change and HbA1c to the simulation.<sup>61</sup>

A key comparison of our model is to the one by Laiteerapong et al.<sup>52</sup> Risks of different levels of hypoglycemia in our model are based on the hypoglycemia risk module developed by Laiteerapong et al. in their patient-level, Monte Carlo-based Markov model. Both models use the baseline UKPDS-OM2 risk equations in modeling health outcomes, but for T2DM patients in the U.S. Considering differences between our model and the one by Laiteerapong et al., a key difference is unlike their or any other model, we specifically estimate risk for MACE and renal events using HRs derived from an NMA of key trials in our population. This HR is applied to the UKPDS-OM2-derived risk equations for specific treatment strategies included in our model. As in ICER's 2019 T2DM review, we believe this approach better accounts for treatment-specific effects on critical outcomes such as MACE and renal outcomes in T2DM patients than the approach used by Laiteerapong et al. or others, who used the unmodified risk equations from the UKPDS-OM2. Other differences between the two models include the NHANES population; we used a more recent population compared to theirs which results in slightly different patient characteristics. As mentioned earlier we modeled a new, previously unmodeled treatment (tirzepatide), our treatment costs were different, we limited patients to only receive insulin after discontinuation or HbA1c increase, and we used an adapted approach to applying utility values when individuals had a history of an event.

Another key comparison of our model is to ICER's 2019 report reviewing oral semaglutide.<sup>39</sup> Other T2DM risk models were considered when preparing the 2022 report on tirzepatide, however the UKPDS-OM2 equations remained the most feasible option and were deemed effective as compared to other available diabetes models when used with CVOT calibration.<sup>133</sup> Updates to the 2019 review included a different set of active treatment comparators and an updated network meta-analysis of treatment effect to reflect tirzepatide clinical trials, additional NHANES patient cohorts, and the addition of change in LDL as an intermediate outcome in the first cycle.

Finally, there have been several additional models published since the publication of ICER's 2019 T2DM report which assess one or more of our comparator therapies, mostly set in countries other than the United States.<sup>131,132,134-136</sup> As an example, Ramos and colleagues published a cost-effectiveness model of empagliflozin compared to sitagliptin and liraglutide in 2021 from a Chinese health care system perspective using the IQVIA Core Diabetes Model (CDM).<sup>131</sup> Like our model, they calibrated their equations to reflect available CVOT outcomes and used indirect treatment comparisons due to lack of head-to-head trial data. They differed from our approach in assuming no lifetime treatment but a switch to insulin as rescue therapy at an 8.5% HbA1c threshold. Results were not comparable due to the therapies included and the baseline Chinese population. Another



study by Capehorn and colleagues likewise used the IQVIA CDM to assess injectable semaglutide versus empagliflozin in a 2021 paper from a United Kingdom health care perspective, also using indirect comparisons via network meta-analysis.<sup>132</sup> Their analysis, like ours, assumed treatment effects in the first year of analysis, then used risk factor progression equations based on equations published by Willis et al.,<sup>61</sup> and had patients initiate insulin therapy when their HbA1c reached a designated threshold. They concluded that semaglutide conferred a lifetime improvement of 0.23 QALYs over empagliflozin, which was comparable to our estimate of 0.25 incremental QALYs for those two therapies.

## F. Potential Budget Impact: Supplemental Information

### **F1. Methods**

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. These results from the cost-effectiveness analyses include the costs of add-on antidiabetic agent (i.e., tirzepatide, injectable semaglutide, empagliflozin), health care resource utilization offsets, and averted health care event offsets. In patients who subsequently progressed to insulin, those insulin costs were attributed to the previously discontinued therapy (e.g., tirzepatide [plus background therapy]). Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs (for instance, due to offsets in major adverse cardiovascular events). All costs were undiscounted and estimated over 1- and 5-year time horizons. The 5-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

To estimate the size of the potential candidate population for treatment, we used inputs for the total US adult population size (~265 million)<sup>68</sup>, overall T2DM prevalence (14.6%)<sup>69</sup>, proportion of patients with diagnosed T2DM (76.7%)<sup>69</sup>, and the proportion of patients having failed background therapy and considering a second-line treatment and thus eligible for tirzepatide (16.2%).<sup>70</sup> Applying these sources results in estimates of 4,800,000 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate tirzepatide treatment in each of the five years, or approximately 960,000 patients per year.

Comparators in the budget impact model included injectable semaglutide, empagliflozin, each added to background therapy, as well as background therapy alone. Conventional therapy consisted of metformin and/or sulfonylureas. Market shares were derived from analyst projections based on primary market research, company reports, and key opinion leader surveys.<sup>71</sup> We set the initial market shares for injectable semaglutide equal to a calculated market share for the GLP-1 RA class (15.1%), while the market share for empagliflozin was set to a calculated market share for the SGLT-2 inhibitor class (12.7%). The remaining market share (72.2%) was attributed background therapy. Market share was captured in proportion to the comparators' initial market shares at a rate of 20% per year, with all patients having switched to tirzepatide by the end of 5-year of the time horizon.

Additionally, we used an estimate of net price (using injectable semaglutide's price as a placeholder), and the three threshold prices (at \$50,000, \$100,000, and \$150,000 per QALY versus injectable semaglutide) in our estimates of tirzepatide's potential budget impact. Injectable semaglutide was chosen as the comparator for threshold price determination in order to align with the HBPBs reported from the cost-effectiveness analyses. ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.<sup>137,138</sup> The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

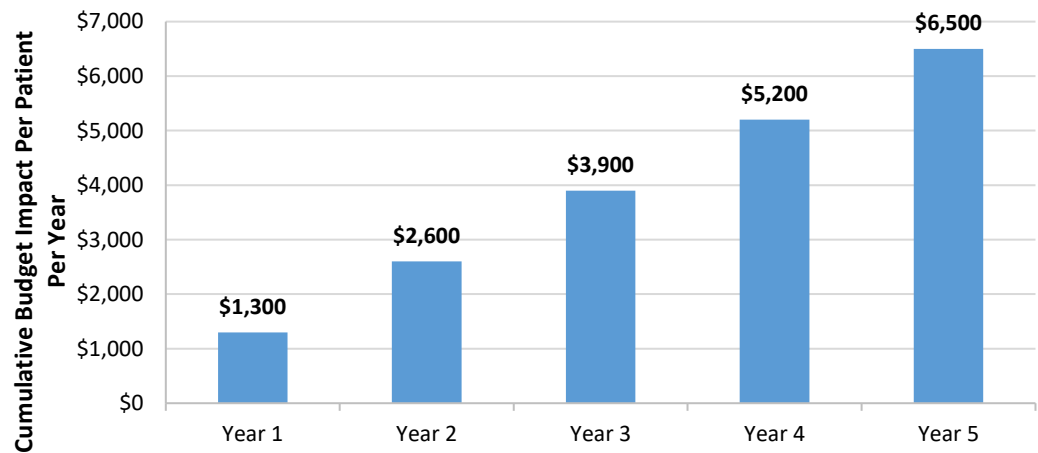
Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in [ICER's methods presentation](#), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent 5-year period for which data were available, and the contribution of spending on retail and facility-based drugs to total health care spending over the most recent 5-year period for which data were available.

For 2021-2022, the five-year annualized potential budget impact [threshold](#) that should trigger policy actions to manage access and affordability is calculated to total approximately \$734 million per year for new drugs.

## F2. Results

Figure F2.1. illustrates the cumulative per-patient budget impact calculations for tirzepatide added to background therapy compared to a mixed market basket consisting of injectable semaglutide, empagliflozin, and background therapy based on the placeholder net price and net prices used within the cost-effectiveness analysis. Switching of eligible adult T2DM patients to tirzepatide resulted in an average potential budgetary impact of approximately \$1,300 per patient per year when assuming our standard uptake of 20% per year. We suggest caution in interpreting the potential budget impact of tirzepatide due to the placeholder annual net price assumed.

**Figure F2.1. Cumulative Annual Per Patient Treated with Tirzepatide at a Placeholder Price of \$4,643.50 per Year\***



\*Placeholder price was assumed. Interpret findings with caution.

Table F2.1. illustrates the average annual per-patient budget impact results in more detail, for tirzepatide’s placeholder price (\$4,643.50\* per year), and the threshold prices to reach \$50,000, \$100,000, and \$150,000 per QALY (\$5,200, \$5,500, and \$5,700, per year, respectively) compared to injectable semaglutide added to background therapy.

**Table F2.1. Average Annual Per-Patient Budget Impact Calculations Over a 5-year Time Horizon**

|   | Average Annual Per-Patient Budget Impact for Each Calculated Price Point |               |                |                |
|---|--|---------------|----------------|----------------|
|   | Placeholder Price*   | \$50,000/QALY | \$100,000/QALY | \$150,000/QALY |
| <b>Tirzepatide and Background Therapy vs. Injectable Semaglutide, Empagliflozin, and Background Therapy</b> | \$1,300  | \$1,800       | \$2,000        | \$2,300        |

QALY: quality-adjusted life year

\*This is an unvalidated placeholder price that is assumed to be equal to the discounted price for injectable semaglutide; injectable semaglutide price is sourced from Red Book, with corresponding discounts used to derive a net price being sourced from SSR Health, LLC <sup>62</sup>

## G. Public Comments

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This section includes summaries of the public comments prepared for the virtual New England CEPAC Public Meeting on January 20, 2022. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found [here](#), beginning at minute 00:00:00. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

**Christian Nguyen, PharmD, MBA, MS, Eli Lilly**  
**Vice President Value Evidence and Outcomes**

Eli Lilly and Company (“Lilly”) has been an innovative global leader in diabetes care for over a century and is committed to meeting the diverse needs of patients. Almost 32 million people in the United States (US) have type 2 diabetes (T2D) (Dugani 2021). Only half of these people meet their blood sugar goals (Fang 2021) and nearly 90% have overweight or obesity (Bramante 2017). Further, T2D disproportionately affects low-income racial and ethnic minorities, at times resulting in higher incidence, prevalence, comorbidities, and complications (CDC 2020, Agardh 2011, Karter 2002). Lilly believes in the potential of tirzepatide to advance equitable care for patients with T2D beyond what is possible with current treatments.

Tirzepatide is an innovative incretin therapy with a novel mechanism of action being studied for the treatment of T2D. Across the SURPASS clinical trial program, treatment with tirzepatide led to clinically meaningful glycemic and body weight reductions across all 3 doses in adults with T2D, with durability of response observed for up to 2 years (Dahl 2021, Del Prato 2021, Frias 2021, Ludvik 2021, Rosenstock 2021). In SURPASS-2, for example, the highest dose delivered unprecedented HbA1c reductions with up to 86% achieving HbA1c <7% and average weight loss of 25 pounds (Frias 2021). Furthermore, tirzepatide’s safety profile was similar to the safety profile of the well-established glucagon-like peptide-1 (GLP-1) receptor agonist (RA) class. This combination of such robust improved glycemic control, significant weight loss, and consistent safety results has not previously been observed with any other pharmacological therapy, making tirzepatide a valuable potential option for patients with T2D.

People with T2D are at significantly greater risk for the development of cardiovascular complications (Hex 2012, Einarson 2018). Surrogate markers of cardiovascular health captured throughout tirzepatide's clinical trial program, including weight reduction, blood pressure reduction, and improvements in the lipid profile, suggest a high likelihood of a cardiovascular benefit (Del Prato 2021). Further, the SURPASS-4 trial demonstrated no excess cardiovascular risk with tirzepatide (hazard ratio: 0.74, 95% confidence interval: 0.51 to 1.08) and a trend towards

cardiovascular benefit (Del Prato 2021, Lilly 2021). Finally, the ongoing SURPASS-CVOT is evaluating the cardiovascular benefit of tirzepatide against dulaglutide, a GLP-1 RA therapy already proven to significantly reduce the risk of major adverse cardiovascular events. This shows Lilly's confidence in this investigational therapy for patients with T2D (NCT04255433). Lilly commends the Institute for Clinical and Economic Review (ICER) for recognizing the importance of cardiovascular outcomes in patient care and thus incorporating the existing cardiovascular data into the assessment.

Outcomes that patients value, such as weight loss and device preference, are important for the long-term successful management of T2D. Weight loss in patients with T2D has been associated with improved clinical, economic and patient-reported outcomes (Boye 2022, Fridman 2020, Karkare 2019). In addition, there is published evidence that patient preferences can vary for different injection devices for T2D treatment (Boye 2019). Device preference can affect adherence to treatment and ultimately patient outcomes (Matza 2019), and this impact should have been incorporated into the economic model. Lilly believes that future updates and value assessments of modern diabetes treatments should more comprehensively capture the impact of weight loss and patient device preference.

Given advances in diabetes therapy, ICER's use of UKPDS OM2 was scientifically inappropriate in this assessment, as it was developed based on clinical data from older therapies. There has been significant innovation in T2D treatment in the past decade, and published evidence suggests that these risk equations are unlikely to capture the long-term benefits of modern treatments (Palmer 2018, Si 2020). Additionally, UKPDS was validated in a patient population from the United Kingdom (UK) and has failed to accurately predict outcomes among more diverse US patient populations. Lilly believes ICER should prioritize using the most relevant data, the most appropriate risk equations, and the most scientifically rigorous models for complex diseases like T2D since results from ICER's assessments can affect patient access to important treatments.

Overall, Lilly believes ICER's assessment captures many of the clinical benefits of tirzepatide, and the comparative value assessment illustrates the strong value that tirzepatide provides to patients with T2D. Lilly acknowledges ICER for their commitment to open communication and engagement with stakeholders in their reviews and believes that tirzepatide can significantly help patients with T2D to meet their treatment goals.

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**Leo Seman, MD, PhD, Boehringer Ingelheim Pharmaceuticals, Inc.**  
**Medical Expert and Executive Director**

This is the second time empagliflozin has been compared by ICER to a member of the GLP1 class of diabetes drugs. Again, we find that the data available have major limitations. It is unclear how to interpret these results given the extremely wide confidence intervals, lack of direct comparison data, and the fact that there are no conclusive cardiorenal outcome studies for tirzepatide, ICER's primary treatment under evaluation.

Empagliflozin and tirzepatide belong to two very different classes of medication, each of which have their own unique benefits and risks. Although there are several overlapping features such as glucose-lowering, weight loss, blood pressure lowering, and lipoprotein modifying effects, they also have many unique features that are not captured by routine biomarkers and thus need to be characterized by outcomes trials. These "unique" properties may play a more important role in the overall health and well-being of this population than is inferred by a few select biomarkers.

ICER's report, however, is driven by imputation from a very narrow collection of biomarkers and without head-to-head trials, data-matching or a conclusive cardio-renal outcomes trial.

For instance, the role of glucose control has been challenged in many large cardiovascular outcome trials, comparing "standard" treatment to aggressive treatment. All of these have been negative trials (ADVANCE, ACCORD, BARI2, etc.), yet the biggest difference and largest driver of this analysis is the greater HbA1c lowering effect of tirzepatide over empagliflozin. An accounting of this difference is imputed, since there are no head-to-head trials comparing the two and since the trials used in the analysis have different baseline A1c ranges, thus putting empagliflozin at a disadvantage. Furthermore, the mean levels of lipids and blood pressure seen in both studies were not in a range that would classify them as significant risk factors as defined by the Framingham risk score and their changes would not be viewed as clinically relevant, questioning whether they should play any role in assessing overall value.

To highlight the need for a true outcomes trial where the benefits are not imputed by biomarkers I use the example of the Empagliflozin REG Outcomes Trial, a well-powered landmark study comparing empagliflozin to standard of care, which demonstrated a 14% reduction in 3-point MACE, driven by a 38% reduction in CV death, also a 35% reduction in decompensated heart failure, and a 39% reduction in renal events, all without remarkable changes in A1c, blood pressure, lipids and weight loss. When assessed by the OM2 risk engine, only about 12% of empagliflozin's effect was predicted, again emphasizing the lack of association between the actual benefits of empagliflozin and changes in these well-known diabetes biomarkers and biometrics.

The ADA has focused on patients with the comorbidities of heart failure, chronic kidney disease, and cardiovascular disease. The ADA recommends that patients with CKD or HF be preferentially

placed on an SGLT2 inhibitor WITH CLINICAL EVIDENCE, not imputed benefit. Empagliflozin falls into this category. A similar statement is made for CVD with GLP1s that have clinical evidence. Tirzepatide could not be included in this category at this time, due to a lack of a proper cardiovascular outcomes study. It is crucial to have a properly powered clinical trial with an adequate time horizon to establish a product's overall benefit, especially when introducing a new unknown entity, like the GIP function in tirzepatide.

A final contention with these evaluation comparisons is that these are not all stand-alone compounds. In the above ADA guideline, if patients' goals are not met, after adding either an SGLT2i or GLP1 the recommendation is to add them together. I find that pitting the two products against each other defies this guidance.

In summary, our specific concerns are as follows:

1. The comparison uses only short-term studies, which cannot determine durability of effectiveness.
2. There is no head-to-head data for a fair comparison
3. There are no powered cardio-renal outcomes trials with tirzepatide for a fair assessment of morbidity and mortality benefit
4. OM2 risk engine cannot account for the inherent benefits of these two newer classes of drugs.

Thank you for your time.

\*Empagliflozin is indicated to reduce the risk of CV death plus hospitalization for heart failure (HHF) in adults with HF and reduced ejection fraction (HFrEF); to reduce the risk of CV death in adults with T2DM and established CV disease; and as an adjunct to diet and exercise to improve glycemic control in adults with T2DM<sup>1</sup>. BI has submitted an application to FDA seeking a new indication based on the HF and preserved ejection fraction (HFpEF) data and, in September 2021, was granted FDA breakthrough therapy designation for HFpEF<sup>2</sup>. Additional research is underway to assess its impact on both chronic kidney disease (CKD) and kidney function decline.

1. Jardiance (empagliflozin)[package insert]. Ridgefield, CT: Boehringer Ingelheim International GmbH; 2021
2. Eli Lilly and Company Press Release. FDA grants Jardiance Breakthrough Therapy designation for heart failure with preserved ejection fraction. 2021; <https://investor.lilly.com/news-releases/news-release-details/fda-grants-jardiance-breakthrough-therapy-designation-heart>.

***Dr. Leo Seman is a full-time employee of Boehringer Ingelheim Pharmaceuticals, Inc.***

**Michael Radin, MD, Novo Nordisk**  
**Executive Director, Diabetes Medical Affairs**

Novo Nordisk is the manufacturer of Ozempic® (injectable semaglutide), which is one of the comparators in this review. Ozempic® is a once-weekly GLP-1 receptor agonist and an important treatment option for adults with type 2 diabetes. The safety and efficacy of Ozempic® has been well-established, with robust clinical data and real-world use. Research includes data in over 11,000 adults, including a cardiovascular outcomes trial that established the direct benefit of Ozempic® for reducing the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. Since its launch in 2018, Ozempic® has helped more than a million Americans — and millions of people worldwide — with type 2 diabetes to lower their hemoglobin A1C while also reducing the risk of major adverse cardiovascular events such as heart attack, stroke, and cardiovascular death for those with type 2 diabetes and cardiovascular disease. And while not indicated for weight loss, Ozempic® has also helped some patients lose weight.

At Novo Nordisk, we welcome research and development that explores new ways of helping people with type 2 diabetes manage their serious disease. However, we would like to strongly reinforce ICER's note of caution in interpreting the findings and conclusions about the comparative and cost-effectiveness of tirzepatide in this report, which uses clinical and other assumptions that are highly uncertain for tirzepatide at this time. In particular, (1) the benefits of tirzepatide on cardiovascular outcomes have not been directly demonstrated in clinical trials, and (2) the impact of the novel dual GIP and GLP-1 receptor agonism mechanism of action of tirzepatide on long-term cardiovascular outcomes is currently unknown.

Cardiovascular disease is the leading cause of death and complications in patients with type 2 diabetes.<sup>1</sup> It contributes substantially to treatment costs for type 2 diabetes, incurring significant burden at both the patient and societal level.<sup>2</sup> As such, we feel it is vital to consider the following points regarding the base-case analysis presented in the cost-effectiveness study.

- The base-case economic analysis presented assumes an equal impact for tirzepatide and injectable semaglutide for composite major adverse cardiovascular events (MACE), a modeling decision based on preliminary biomarker signals from the SURPASS-4 study. This interpretation results in an assumption of greater health benefit for tirzepatide vs injectable semaglutide.
- However, as appropriately stated in the Evidence Report, the ICER clinical evidence review team chose not to extrapolate the cardiovascular outcomes data for GLP-1 RAs to tirzepatide in generating the clinical evidence rating. In support of this decision, the review noted that cardiovascular benefit is not uniform across the GLP-1 RA class. In addition, there is uncertainty with regards to cardiovascular effects of the dual GIP/GLP-1 mechanism

of action. Thus, the clinical evidence assessment and economic model are conflicting in the assumed benefit of tirzepatide on MACE.

- There is a scenario analysis in the Evidence Report where no direct benefit on a reduction in MACE events was assumed for tirzepatide. In this analysis, tirzepatide resulted in a lower net health benefit relative to injectable semaglutide. This scenario was the base case in the previous version of the draft evidence report.
- Because tirzepatide has not established a MACE benefit, we believe that the analysis which assumes no MACE benefit for tirzepatide should be the base case, as in the previous version of the draft report. Making this change will align the economic analysis with the clinical evidence review and assessment. Alternatively, at a minimum, the two cost-effectiveness results, both with and without assigning a MACE benefit to tirzepatide, should be weighed equally in the final evidence report.

Novo Nordisk appreciates the active engagement with ICER throughout the course of this review, and we look forward to ongoing collaboration to help drive better outcomes for people living with type 2 diabetes.

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***Dr. Michael Radin is a full-time employee of Novo Nordisk***

## H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the January 20, 2022 Public meeting of the New England CEPAC.

**Table H1. ICER Staff and Consultants and COI Disclosures**

| ICER Staff and Consultants   |  |
|--|--|
| <b>Elizabeth Brouwer, PhD, MPH*</b><br>Research Scientist, The CHOICE Institute, University of Washington  | <b>Grace A. Lin, MD*</b><br>Medical Director for Health Technology Assessment, ICER<br>Associate Professor of Medicine and Health Policy,<br>University of California, San Francisco |
| <b>Jon D. Campbell, PhD, MS*</b><br>Senior Vice President for Health Economics, ICER                       | <b>Ashton Moradi, PharmD, MS*</b><br>Health Economist, ICER  |
| <b>Yilin Chen, MPH, PhD student*</b><br>PhD Student, The CHOICE Institute, University of Washington        | <b>Dmitriy Nikitin, MSPH*</b><br>Research Lead, Evidence Synthesis, ICER   |
| <b>Kelsey Gosselin, MA*</b><br>Program Manager, ICER   | <b>Steven D. Pearson, MD, MSc*</b><br>President, ICER  |
| <b>Ryan N. Hansen, PharmD, PhD*</b><br>Associate Professor, The CHOICE Institute, University of Washington | <b>Liis Shea, MA*</b><br>Program Director, ICER  |
| <b>Serina Herron-Smith, BA*</b><br>Senior Research Assistant, Evidence Synthesis, ICER                     | <b>Grace Sternklar, BS*</b><br>Program Coordinator, ICER   |

\*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of \$10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

**Table H2. New England CEPAC Panel Member Participants and COI Disclosures**

| Participating Members of CEPAC  |   |
|---|---|
| <b>Rob Aseltine, PhD*</b><br>Professor and Chair, Division of Behavioral Sciences and Community Health Director, Center for Population Health, UCONN Health               | <b>Aaron Mitchell, MD, MPH*</b><br>Assistant Attending,<br>Memorial Sloan Kettering Cancer Center   |
| <b>Austin Frakt, PhD*</b><br>Director, Partnered Evidence-Based Policy Resource Center, VA Boston Healthcare System; Professor, Boston University School of Public Health | <b>Eleftherios Mylonakis, MD, PhD, FIDSA*</b><br>Chief of Infectious Diseases Division, Dean Professor of Medicine, Warren Alpert Medical School of Brown University                            |
| <b>Marthe Gold, MD, MPH*</b><br>Logan Professor Emerita, CUNY School of Medicine  | <b>Stephanie Nichols, PharmD, BCPS, BCPP, FCCP*</b><br>Associate Professor of Pharmacy Practice, University of New England College of Pharmacy  |
| <b>Megan Golden, JD*</b><br>Co-Director, Mission:Cure   | <b>Jason L. Schwartz, PhD*</b><br>Assistant Professor, Department of Health Policy and Management, Yale School of Public Health   |
| <b>Stephen Kogut, PhD, MBA, RPh*</b><br>Professor of Pharmacy Practice, University of Rhode Island College of Pharmacy  | <b>Jason Wasfy, MD, MPhil (Chair)*</b><br>Director, Quality and Outcomes Research, Massachusetts General Hospital Heart Center; Medical Director, Massachusetts General Physicians Organization |
| <b>Donald Kreis, JD*</b><br>Consumer Advocate, New Hampshire Office of the Consumer Advocate  | <b>Rev. Albert Whittaker, MA*</b><br>Interim Pastor, St. Mark Congregational Church<br>Consultant, Health Integration and Equity  |
| <b>Greg Low, RPh, PhD*</b><br>Program Director, MGPO Pharmacy Quality and Utilization Program, Massachusetts General Hospital   |   |

\*No relevant conflicts of interest to disclose, defined as more than \$10,000 in healthcare company stock or more than \$5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

**Table H3. Policy Roundtable Participants and COI Disclosures**

| <b>Policy Roundtable Participant</b>  | <b>Conflict of Interest</b>   |
|---|---|
| <b>Lizzette Cambron, PhD</b><br>Type 2 Diabetes Patient and Advocate  | None.   |
| <b>Mohammad Dar, MD</b><br>Senior Medical Director,<br>MassHealth   | Mohammad Dar practices as an internist in the VA Boston Healthcare system.  |
| <b>Bonnie Donato, PhD</b><br>Executive Director, HEOR VDT CV-<br>MET & Respiratory, Boehringer<br>Ingelheim   | Bonnie Donato is an employee of Boehringer Ingelheim and has had equity interest from Astra Zeneca.   |
| <b>Sarah Kim, MD</b><br>Associate Clinical Professor,<br>University of California San<br>Francisco  | None.   |
| <b>Liz Leff</b><br>Senior Corporate Relations<br>Director, National Kidney<br>Foundation  | The National Kidney Foundation receives less than 25% of its funding from pharmaceutical manufacturers, including from Novo Nordisk and the BI-Lilly Diabetes Alliance.   |
| <b>Joanna Mitri, MD, MS</b><br>Medical Director, Global<br>Education and Care Division<br>Joslin Diabetes Center, Assistant<br>Professor, Harvard Medical<br>School | Dr. Mitri has received manufacturer support of research in the clinical area of this meeting, and her institution conducts clinical trials and educational programs that may be supported by health care companies. A household member of Dr. Mitri's has received consulting fees from health care companies including AbbVie, Roche, Janssen Pharmaceuticals, Pharmacyclics, and BeiGene. |
| <b>William Riesner, JD, MBA</b><br>Director   | William Riesner is a full-time employee at Eli Lilly.   |